THE

AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

MARCH, 1936

ORIGINAL ARTICLES.

PNEUMOCOCCUS TYPE III PNEUMONIA.

AN ANALYSIS OF 500 CASES.

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PNEUMOCOCCUS Type III pneumonia has always aroused the interest of medical men, partly because of the peculiar morphologic, biologic and chemical properties of pneumococcus Type III, but chiefly because of the generally recognized severity of this type of pneumonia. There, however, is comparatively little in the medical literature concerning Type III pneumonia as a clinical entity. Among the statistical studies which deal with the incidence and death rate for the various types of pneumonia should be mentioned the studies of Dochez and Gillespie,[1] Dochez and Avery,[2] Cole,[3] and Bullowa.[4] In 1927, Cecil, Baldwin and Larsen,[5] in a statistical study on 2000 typed cases of lobar pneumonia, pointed out certain clinical features of the various types. In this article it was first brought out that Type III pneumonia was particularly common in elderly people and that the incidence of this type was higher in

women than in men. It was also shown that Type III pneumonia was especially prevalent in patients with some chronic systemic disease. All writers on this subject are agreed that Type III pneumonia has in general a much lower incidence than Type I or Type II infections, and that the death rate is high (in most reports from 40 to 50%). Blake,[6] in a recent report on 122 cases of Type III pneumonia studied in the wards of the New Haven Hospital, corroborates the findings of Cecil, Baldwin and Larsen, and stresses the fact that, though Type III pneumonia has a high death rate, it is no more fatal than other types when it occurs in young and healthy people.

In Blake and Cecil's[7] experimental Type III pneumonia in monkeys (intratracheal injection of small doses of pneumococcus Type III culture), the disease ran a characteristic mild course. More recently, Francis and Terrell[8] have produced experimental Type III pneumonia in monkeys by insufflation of pneumococcus Type III culture deep into the trachea and bronchus by means of a soft rubber catheter. They found that the severity of the disease was roughly proportional to the amount of culture injected and that the death rate for experimental Type III pneumonia in monkeys was directly proportional to the height of the septicemia accompanying the pneumonia.

Sugg[9] and his co-workers were the first to call attention to an "atypical" Type III pneumococcus. They found it to be closely related immunologically to typical strains, and pointed out how readily it could be confused with the latter in routine typing because of the high degree of cross-agglutination which may occur between the two types with some diagnostic serums. In the revised classification of pneumococci by Cooper,[10] the atypical pneumococcus Type III has been designated pneumococcus Type VIII.

Finland and Sutliff[11] have recently contributed an interesting comparative study of the clinical features of pneumonia as produced by pneumococcus Type III and Type VIII respectively. For example, they show that Type VIII pneumonia, like Type III, is much more common in females than in males, and that chronic disease was a common predisposing factor in both Type III and Type VIII infections.

The present study is based on material which has been collected during the past decade or more in the wards of Bellevue Hospital, and is really a continuation of previously published studies on the various types of pneumonia (Cecil and Plummer[12]). In addition to material from the adult medical wards, 9 cases of Type III pneumonia from the pediatric service at Bellevue Hospital are included.

Incidence. As already mentioned, pneumococcus Type III pneumonia has a much lower incidence than either Type I or Type II infections (Table 1). In 4310 pneumococcal pneumonias,

Type I infections were the most frequent (32.1% of the whole series); Type II ranked next with 23%, while Type III comprised only 11.1%.

TABLE 1.—INCIDENCE OF DOMINANT TYPES OF LOBAR PNEUMONIA IN BELLEVUE HOSPITAL, 1920–1931.*

Type of pneumococcus.	No. of cases.	Incidence, %.
Type I	1384	32.1
Type II	991	23.0
Type III	477	11.1
Misc. types	1458	33.8

* 1925–1926 cases are omitted from this series.

A comparison of the incidence of Type III pneumonia in Bellevue Hospital and in other institutions in New York and New Haven (Table 2), reveals that the incidence of Type III pneumonia is remarkably constant in three large New York hospitals. A higher incidence was found in the New Haven Hospital, and may be explained by differences in environment, type of patient admitted, etc. When the total of 765 Type III cases included in these reports is averaged, the incidence of Type III pneumonia is 11.8% of the entire pneumococcal series. Approximately 1 in every 8 cases of lobar pneumonia is a Type III infection.

TABLE 2.—COMPARATIVE INCIDENCE OF DOMINANT TYPES OF PNEUMONIA IN FOUR HOSPITALS.

Type of pneumococcus.	Bellevue Hospital. (Cecil.)		Rockefeller Hospital. (Cole.)		Harlem Hospital. (Bullowa.)		New Haven Hospital. (Blake.)	
	No. of cases.	Incidence, %.	No. of cases.	Incidence, %.	No. of cases.	Incidence, %.	No. of cases.	Incidence, %.
Type I	1384	32.1	403	36.3	112	31.0	194	32.0
Type II	991	23.0	249	22.4	69	19.0	79	13.0
Type III	477	11.1	123	11.1	43	12.0	122	20.0
Misc. types	1438	33.8	335	30.2	141	38.0	211	35.0

Incidence of Type III Pneumonia in Children. In 329 cases of pneumonia in children at Bellevue Hospital, Raia, Plummer and Shultz[13] found only 10 cases of Type III pneumonia. All 10 of these occurred in children under 3 years.

Incidence According to Age. Cecil, Baldwin and Larsen[5] were the first to point out that Type III pneumonia constituted 33.7% of all pneumococcal pneumonias in patients over 60 years, which was almost twice as high as the incidence of Type I or Type II pneumonia in this age group. If one considers *only* the Types I, II and III infections in the present series, 45.8% of all cases over 60 years were Type III infections, while if *all* types are included, pneumococcus Type III constituted 32.8% of the cases over 60 (Table 3). In contrast to these figures, in patients under 50, only 9.4% were suffering from Type III infections.

TABLE 3.—INCIDENCE OF TYPES IN RELATION TO AGE.

Type of pneumococcus.	Under 50 years.		Over 50 years.		Over 60 years.	
	Cases.	%.	Cases.	%.	Cases.	%.
Type I	1056	33.8	194	22.6	63	18.8
Type II	785	25.2	249	28.9	77	22.9
Type III	292	9.4	208	24.2	110	32.8
Misc. types	986	31.6	209	24.3	85	25.5

Blake found the preponderance of Type III infections even more marked in elderly patients. In his series, 70% of all patients over 60 years with Types I, II or III pneumonia were Type III infections.

Figure 1, based on our own cases in Bellevue Hospital, illustrates graphically the comparative age incidence of Types I, II and III pneumonia according to decades.

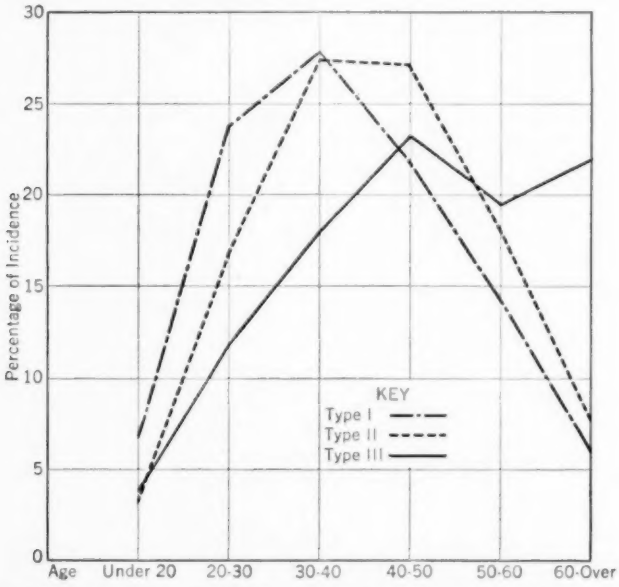

FIG. 1.—Incidence of pneumococcus Types I, II and III pneumonia in relation to age.

It will be noted that the incidence curves of Type I and II pneumonia run almost parallel, both reaching their highest points between 30 and 50, and falling off rapidly during the later decades of life. On the other hand, the incidence curve of Type III pneumonia ascends more gradually, reaching its highest point at the age of 50 and maintaining a high level during the remaining decades of life. Of the adult Type III pneumonias, 64.8% occurred in patients past 40. This figure compares favorably with that of Finland and Sutliff, who found 69% of their Type III infections in patients over 40.

Incidence of Type III Pneumonia According to Sex. In the

present study the number of Type III pneumonias in males exceeds that in females (392, or 78%, males, and 108, or 22%, females). In statistical studies all types of lobar pneumonia appear to occur more frequently in males than in females, but this apparent preponderance of males may be due, at least in part, to the fact that there are always more male than female patients in city hospitals. Females, however, are apparently more susceptible to Type III infections than males, for the *incidence per cent* is 18.2% for females, as compared with 11.6% for males (Table 4). This is in sharp

TABLE 4.—INCIDENCE OF TYPES IN RELATION TO SEX.

Type of pneumococcus.	Total males.		Total females.	
	Cases.	%.	Cases.	%.
Type I	1108	32.7	142	23.9
Type II	956	28.2	78	13.1
Type III	392	11.6	108	18.2
Misc. types	929	27.5	266	44.8

contrast to Type I and Type II infections, where the incidence per cent for the two latter types is considerably higher for males than for females.

Incidence of Type III Pneumonia in Relation to Age and Sex. In Table 5 the combined influence of age and sex on the incidence of Type III pneumonia is indicated.

TABLE 5.—INCIDENCE OF TYPES IN RELATION TO AGE AND SEX.

Type of pneumococcus.	Males under 50 years.		Females under 50 years.		Males over 50 years.		Females over 50 years.	
	Cases.	%.	Cases.	%.	Cases.	%.	Cases.	%.
Type I	930	35.0	126	26.7	178	25.0	16	13.0
Type II	720	27.2	65	13.7	236	33.1	13	10.6
Type III	231	8.8	66	13.6	138	19.4	45	36.6
Misc. types	769	29.0	217	46.0	160	22.5	49	39.8

In both groups, that is, in patients under 50 as well as in those over 50, Type III pneumonia is twice as common in women as in men, and it is four times as common in women over 50 (36.6%) as it is in men under 50 (8.8%). This table further shows that in females over 50, infections with Type III and the miscellaneous types cause 76.4% of all pneumonias, while in males under 50 they cause only 37.8% of the cases. These latter figures have considerable significance with respect to serum therapy; two-thirds of the pneumonias in men under 50 will be Type I or Type II infections and, therefore, amenable to serum treatment.

Incidence by Season. There appears to be very little difference so far as seasonal distribution is concerned between the incidence of the three dominant types of pneumonia. (Fig. 2.)

In all three types the incidence is highest in January, February and March. Then begins a rapid descent, striking the lowest point in early summer and continuing there through September.

In October the curves begin to rise again; 79% of all the Type III pneumonias were admitted to the hospital between December and May, inclusive.

Relation of Type III Pneumonia to Chronic Disease. Pneumococcus Type III pneumonia is two to three times as apt to occur in individuals who are already the victim of some chronic disease as are Types I and II pneumonias. This was first pointed out by Cecil, Baldwin and Larsen, and has recently been confirmed by Blake who found that 79 of 119 cases of Type III pneumonia were victims of some chronic systemic condition. Blake points out that this was not entirely the result of advancing years, as 19 of 32 patients with Type III pneumonia between 20 and 50 years suffered from chronic disease.

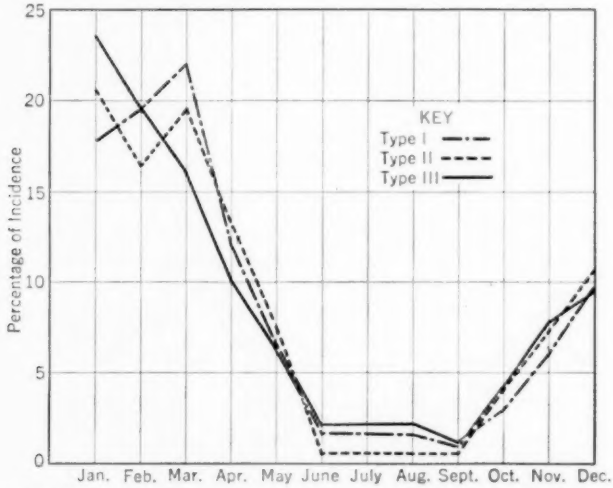

FIG. 2.—Incidence of pneumococcus Types I, II and III pneumonia in relation to season.

In the present study, 49.9% of the Type III patients were afflicted with some chronic malady, a considerably higher proportion than for either Type I or Type II infections (Table 10). Of these cases with chronic disease, 24 were under 30 years. Alcoholism and degenerative cardiovascular disease lead the list. The mortality in chronic alcoholic patients was very high—almost 50%. There was a death rate of 77% for patients with chronic cardiovascular disease.

Clinical Features. Clinically Type III pneumonia shows no special characteristic features which would differentiate it from the other types of pneumonia. The onset was described as sudden in 52% of the cases. The two most common initial symptoms were chill and pain in the chest. It was found that the right lung only

was involved in 226 cases, as compared to 168 with left-sided consolidation. In single lobe involvement the right lower lobe was most frequently affected.

Duration of Disease. Cecil, Baldwin and Larsen, in their study of 2000 typed pneumonias, found that pneumococcus Type III pneumonia ran, on an average, a somewhat longer course than either Type I or Type II infections. The average duration of the Type III series was 9.1 days, as compared with an average duration of 8.8 days for Type I pneumonia and 8.6 days for Type II pneumonia. Blake found that in Type III pneumonia affecting individuals past 50, that is, during the period of high susceptibility, the disease ran a longer course than it did in those under 50, and that in the elderly group recovery was nearly always by lysis rather than by crisis.

In the present study, termination, if by crisis, usually occurred before the eighth day; if by lysis, on or after the eighth day. Crisis occurred in 153 cases *under* 50 years (52.3%), as compared with only 32 cases *over* 50 years (15.3%). It was found that complications occurred in only 4.8% of patients who recovered by crisis, as compared with 19.7% of patients who recovered by lysis.

Bacteriemia. Blood cultures were taken on one or more occasions in 198 cases. Positive cultures were found in 55 (29.4%). This figure approximates closely the Harlem Hospital figures as reported by Rosenbluth[14] (25%) and those of Finland and Sutliff (34%). Blake, reported bacteriemia in only 8% of his Type III series.

Eight of our Type III patients with positive blood cultures recovered. Two of these showed positive plate cultures, while the others were positive in broth only. One patient, a male, aged 41, and an alcoholic, had 100 colonies of pneumococcus Type III per cc. of blood, and recovered. In the fatal cases, bacteriemia was present before the fifth day in 43 of the 47 cases. In 4 septic cases the blood cultures became negative before death. All of the septic patients who recovered were under 50 years of age. Invasion of the blood stream by the hemolytic streptococcus was observed in 3 patients with Type III pneumonia, and 1 of these recovered.

It is interesting to compare the incidence of bacteriemia in Type III pneumonia, with its incidence in Type I and Type II infections, as observed in the Bellevue Hospital studies (Table 6). In our experience the incidence of bacteriemia in Type III pneumonia is about the same as that for Type I cases. Both types show a considerably lower incidence of bacteriemia than Type II infections. The death rate for all bacteriemic cases is very high. It is noteworthy, however, that while the incidence of bacteriemia in Type I and Type II pneumonia coincides closely with the death rate for these types, respectively, in Type III infections the death rate is considerably higher than the incidence of bacteriemia. In other words, some patients with Type III pneumonia die without sepsis.

TABLE 6.—COMPARATIVE INCIDENCE OF BACTEREMIA IN THE DOMINANT TYPES OF PNEUMONIA.

Type of pneumococcus.	Cases cultured.	Bacteriemia, %.	Death rate, %.	
			Bacteremic cases.	Entire series.
Type I	64	29.7	66.7	28.2*
Type II	133	51.1	87.5	48.8*
Type III	187	29.4	85.4	42.2*

* None received serum.

Complications. The complications of Type III pneumonia show no special features. A study of Table 7 reveals that the complications in the present series of 500 Type III pneumonias occurred in about the usual incidence rate.

TABLE 7.—COMPLICATIONS IN PNEUMOCOCCUS TYPE III PNEUMONIA.

Complications.	No. of cases.	Incidence, %.	Died.	Fatality, %.
Empyema	28	5.6	13	46.4
Meningitis	4	0.8	4	100.0
Endocarditis	0	0	0	
Pericarditis	3	0.6	3	100.0
Arthritis	2	0.4	1	50.0
Phlebitis	2	0.4	1	50.0
Otitis*	10	2.0	0	
Cardiac irregularity	14	2.8	11	78.6
Delayed resolution	2	0.4	0	
Cellulitis	6	1.2	1	16.7
Lung abscess	1	0.2	1	100.0
Pleural effusion	7	1.4	5	71.4

* Eight of these cases were in children.

It was shown by Cecil, Baldwin and Larsen that Type I pneumonia is more frequently complicated by empyema than any of the other pneumococcal types. These investigators found that empyema occurred in almost 7% of their Type I cases. In the present series of Type III cases, empyema developed in 5.6% of the series, which is just about the usual incidence for empyema in pneumonia as a whole. Empyema was most common in bacteremic cases, as indicated in Table 8. Of the 8 bacteriemic patients who developed empyema, only 2 recovered, while of 6 non-bacteremic cases, 4 recovered.

TABLE 8.—INCIDENCE OF EMPYEMA IN BACTEREMIC AND NON-BACTEREMIC CASES.

	No. of cases.	Cases with empyema.	Incidence, %.	Death rate, %.
Bacteremic patients	55	8	14.5	75.0
Non-bacteremic patients	132	6	4.5	33.3

It is interesting to note the absence of endocarditis as a complication in Type III pneumonia in the present series. Blake encountered only 1 case of Type III endocarditis in his series of 111 cases. Necropsies on all our fatal cases would no doubt have revealed a terminal pneumococcal endocarditis in a few cases; but even admitting this source of error, the infrequence of endocardial involvement in Type III pneumonia is probably due to the relatively low incidence of bacteremia in Type III cases. Cecil and Plummer[12] found that the highest incidence of pneumococcal endocarditis was

in Type II pneumonia; in other words, in the type that shows the highest incidence of pneumococcal bacteremia. There appears to be a definite relationship between the incidence of bacteremia and the incidence of endocarditis as a complication.

Death Rate. It has already been shown (Table 6) that the death rate for this series of 500 cases of Type III pneumonia was 42.2%, a figure which agrees closely with that reported by other investigators (Blake, 44.3%; Cole, 43%; Bullowa, 40%). Finland and Sutliff, however, report a much higher rate in their series of 225 cases of Type III pneumonia (60%). In our experience, Type III pneumonia, fatal as it is, ranks second in virulence, being surpassed by a small margin by pneumococcus Type II pneumonia, with a death rate of 48.8%. Of the three dominant types, Type I has the lowest death rate—in our series, 28.2% for cases that received no serum. The figures for both Type I and Type II infections would be considerably lower for serum-treated cases. We have already pointed out how much higher the rate becomes for all three types when only bacteremic cases are considered. Type III cases with positive blood cultures had a death rate of 85.4%, which was almost three times higher than that for patients with negative cultures. Finland and Sutliff reported 100% mortality for their septic Type III series. It was also apparent in our group that as the age increased the tendency to bacteremia increased, and this may explain in part the high fatality rate in patients over 50 years.

Over a period of more than a decade there were 214 deaths from Type III pneumonia in Bellevue Hospital. Some of our Type III patients received antipneumococcal serum in various forms, but as it never appeared to have the slightest clinical effect, there is no reason to believe that its use affected the death rate in the Type III series in any way. During the same period there were 501 deaths from Type II and 222 deaths from Type I pneumonia. It is clear therefore that, although Type III pneumococcus is responsible for only 10 to 12% of all pneumococcal pneumonias, it contributes its share toward the death rate of pneumonia. It is interesting to analyze these deaths from pneumonia still further, particularly with reference to age, sex and chronic systemic disease.

Cecil, Baldwin and Larsen first called attention to the importance of age in the death rate of Type III pneumonia: Under 40 it is a comparatively mild infection, showing a death rate actually lower than in some other types; after 40 the death rate rises rapidly, but not more rapidly than that for Type II pneumonia. It has long been known, of course, that all types of pneumonia show a steadily increasing death rate for each decade. Apparently the reason for the high death rate in Type III pneumonia as a whole is that a very large proportion of Type III pneumonias occur in the later decades of life. The relation of age to mortality rate in Type III

pneumonia is shown graphically in Fig. 3. The curves for Type I and Type II pneumonias are included for comparison. From these curves it is clear that, as pointed out by Cecil, Baldwin and Larsen and corroborated by Blake, the death rate for Type III patients under 40 is little if any higher than that for Type I and Type II cases. After 40, the death rate for both Type II and Type III infections rises very rapidly, while in Type I cases the rise is more gradual.

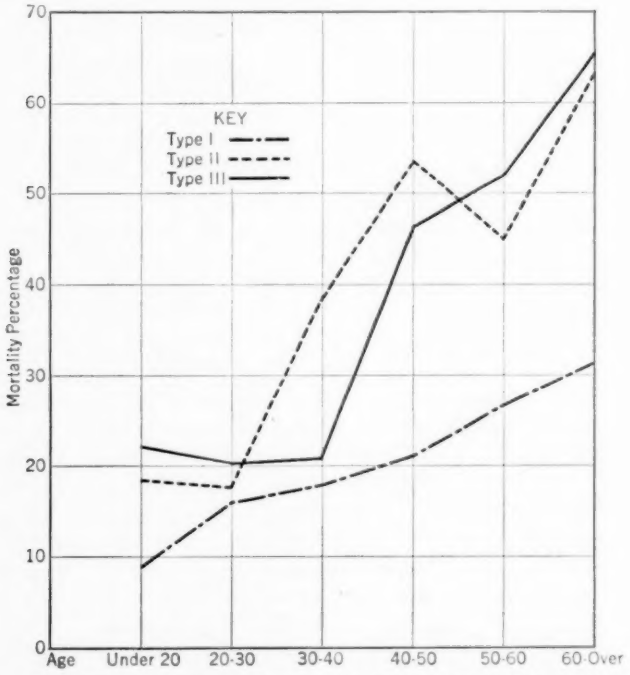

FIG. 3.—Mortality rates for pneumococcus Types I, II and III in relation to age.

In Table 9, it is surprising to note what a low percentage of the total deaths from pneumonia are caused by pneumococcus Type III in *males* under 50 (9.5%). On the other hand, in females under 50,

TABLE 9.—ANALYSIS OF TOTAL DEATHS FROM PNEUMONIA IN BELLEVUE HOSPITAL (1920–1932) WITH REFERENCE TO AGE AND SEX.

Type of pneumococcus	Males under 50 years.		Males over 50 years.		Females under 50 years.		Females over 50 years.	
	Deaths.	%.	Deaths.	%.	Deaths.	%.	Deaths.	%.
Type I . .	172	25.3	78	18.5	20	21.1	6	8.2
Type II . .	266	39.2	139	33.6	20	21.1	7	9.6
Type III . .	62	9.5	93	22.5	24	25.2	30	41.1
Misc. types .	177	26.0	105	25.4	31	32.6	30	41.1

Type III pneumonia was responsible for 25.2% of all deaths, and in females *over* 50, pneumococcus Type III wrought its greatest

havoc, causing 41.1% of all pneumonia deaths in this age-sex group. In this latter group, Type I and Type II pneumococcus played a comparatively insignificant rôle as a cause of death.

TABLE 10.—INCIDENCE AND DEATH RATE FOR PNEUMONIAS WITH AND WITHOUT SYSTEMIC DISEASE.

Pneumonia.	With systemic disease.	Death rate.
Type I	20.4	32.0
Type II	33.0	49.0
Type III	49.6	53.6

Pneumonia.	Without systemic disease.	Death rate.
Type I	79.6	18.5
Type II	67.0	41.9
Type III	50.4	32.1

As would be expected, the high frequency of chronic disease in Type III pneumonia adds greatly to the seriousness of the prognosis. For example, Cecil and his co-workers found the death rate for 48 Type III pneumonias not associated with chronic disease was only 8.5%, whereas in 83 cases that were associated with chronic disease the death rate was 66.4%. In Blake's series, where the association of Type III with chronic disease was high even in the young, 19 of the 32 patients between 20 and 50 years had some form of chronic disease. Of these 19, 12 died, while of the 13 in previous good health, only 2 died. In Table 10, the incidence and death rate of Type III cases associated with systemic disease is indicated. For comparative purposes the death rate for cases without systemic disease is also shown. It is evident from a study of these figures that Type III pneumonia is not more serious than other types when it attacks people who have previously enjoyed good health. It becomes serious, however, when it affects those afflicted with some chronic disease or those who have attained old age. As Blake well expresses it, "Pneumococcus Type III pneumonia is a highly fatal specific infectious disease, due in general not to a highly infectious organism that attacks and kills a healthy host, but rather to a debilitated or senescent host who succumbs to what is a relatively mild and uncommon infection in the young and vigorous."

Discussion. In the preceding paragraphs we have attempted to show that Type III pneumonia has certain very definite characteristics which distinguish it sharply from other types. These special characteristics are no doubt due to the inherent qualities of pneumococcus Type III. This organism was originally spoken of as the Streptococcus mucosus, but was finally classified, and rightly so, as a pneumococcus. Dochez and Avery were the first to designate it pneumococcus Type III. The most important investigations into the nature of Type III pneumococcus are those of Avery[15] and his co-workers who have brought out some very interesting facts concerning the polysaccharid which is contained in the capsule of pneumococcus Type III. This capsular polysaccharid which is often referred to as the "soluble specific substance" varies for each

type of pneumococcus and in fact, determines the specificity of each type. In 1931, DuBos and Avery[16] reported the discovery of a motile spore-bearing pleomorphic bacillus which had been isolated from peet oil and which had the ability of decomposing the specific polysaccharid of Type III pneumococcus. This specific action on the polysaccharid is due to an endocellular enzyme generated by the pleomorphic bacillus. The enzyme can be extracted by autolysis of the bacterial cells. In sterile solution the enzyme has the same specific action as do the organisms from which it is derived, decomposing the capsular polysaccharid of Type III pneumococcus, but having no effect on the polysaccharid of other pneumococcal types. In a subsequent study Avery and DuBos[17] showed that the bacterial enzyme which decomposes the polysaccharid of Type III pneumococcus *in vitro* also destroys the capsules of the living organisms growing in media and in the animal body, and that potent preparations of this enzyme would protect mice against infection with virulent Type III pneumococcus. Furthermore, the enzyme was found to exert curative action in mice infected intraperitoneally with pneumococcus Type III, even when the enzyme was injected 12 to 18 hours after infection. Goodner and DuBos[18] were able to save rabbits infected intradermally with pneumococcus Type III by injecting the enzyme intravenously 24 hours after inoculation with the culture. They noted that the amount of enzyme necessary to bring about the recovery of the infected rabbit bears a definite relationship to the severity of the infection as gauged by the number of pneumococci present in the circulating blood. Finally, in a recent article, Avery and his co-workers have demonstrated clearly the therapeutic value of the specific enzyme upon experimental Type III pneumococcus pneumonia in monkeys. Treatment with the enzyme was followed by cessation of spread of the pneumonic lesion, sterilization of the blood and early recovery, except in animals in which the severity of the disease was extreme. These authors found that in monkeys, as in rabbits, the therapeutic value of the enzyme was directly proportional to the number of pneumococci present in the circulating blood of the infected animal.

These studies have great theoretic and practical importance. They open up an entirely new line of attack against pneumococcal infections in general, and they possess great practical importance because at the present time we have no satisfactory serum treatment for Type III infections. The writer was never able to save monkeys infected with lethal doses of Type III pneumococcus by the administration of Huntoon's pneumococcus antibody solution. Cecil and Larsen[19] showed that pneumococcus antibody solution, though it affected favorably the death rate in both Type I and Type II pneumonias, had no effect whatever on the death rate in Type III pneumonia. A few years later, Cecil and Sutliff[20] had similar results with Felton's concentrated antipneumococcus serum. On

the other hand, Watson and Cooper,[21] producing intradermal lesions and frequent bacteremia in rabbits by the intradermal inoculation of Type III pneumococci, found that such bacteremia was checked and the rabbits protected by suitable amounts of Type III concentrated antiserum given intravenously 24 hours after the infecting doses. Furthermore, they found that the amount of Type III antiserum necessary to protect rabbits inoculated intradermally with virulent Type III cultures was not appreciably greater than the amount of Type I antiserum required to protect against Type I. The inconsistency between the results obtained by Watson and Cooper on rabbits and those obtained by Cecil on monkeys is not so striking as might at first appear. The former workers used a serum which contained 1000 protection units per cc. against a stock Type III strain. The serums which we used for our monkey experiments and for the clinical studies on patients possessed a much lower potency.

The whole problem of controlling Type III pneumonia by prophylactic immunization or by the use of a highly efficient serum centers around the difficulty of stimulating a high titer of immune bodies by the injection of killed or living Type III pneumococci. For example, Cecil and Steffen[22] found that 3 subcutaneous injections of pneumococcus Type I or Type II vaccine would confer on monkeys a complete immunity against pneumococcal pneumonia of homologous types. However, 3 subcutaneous injections of pneumococcus Type III vaccine gave a complete protection against Type III pneumonia in only 4 out of 8 monkeys vaccinated. The same investigators did succeed in vaccinating monkeys against pneumococcus Type III pneumonia by giving Type III vaccine in large doses intratracheally. Ross[23] was able to protect rats against pneumococcus Type III pneumonia by feeding them Type III pneumococcus vaccine. Cecil and Austin,[24] studying the blood serum of 8 human volunteers who received a polyvalent pneumococcus vaccine subcutaneously, tested their serums 7 days later for agglutinins and protective bodies. A number of the vaccinated men developed agglutinins for Type I and Type II pneumococcus, but none for Type III. In a similar way, all of the men developed protective bodies against Type I and Type II pneumococcus, but only 3 of the 8 showed any protection against Type III.

One is justified in making the inference that immunity against Type III pneumococcus is difficult to acquire by either artificial or natural methods. The not unusual recurrence of Type III pneumonia in the same individual is another indication that this is true.

The treatment of pneumococcus Type III pneumonia with homologous convalescent serum has been tried by Beebe and Sutliff.[25] The patient was a male, aged 55, and he received his first injection of Type III convalescent serum (120 cc.) on the fourth day of his disease. On the fifth day he received 190 cc. of Type III convales-

cent serum. The Type III serum administered showed only slight protective power for mice, but had moderately high agglutinins and precipitin titers. In spite of the serum administered, the patient developed a positive blood culture and died on the sixth day of his disease. Barach treated 6 cases of pneumococcus Type III pneumonia by transfusing them with blood from donors who had been immunized against pneumococcus Type III. The serums employed all showed a fairly high titer of protective bodies as tested on mice. Four of the 6 patients had a Type III bacteremia, and all died. The 2 Type III cases with sterile blood cultures survived. According to Barach,[26] the immediate effect of the transfusion on the clinical condition of the patient was negligible.

Summary. 1. Pneumococcus Type III ranks third as an exciting agent in lobar pneumonia, causing 11.8% of all pneumococcal pneumonias. It is surpassed only by pneumococcus Type I and Type II in respect to prevalence.

2. The incidence of pneumococcus Type III pneumonia increases with age. In the present series pneumococcus Type III was responsible for 32.8% of all pneumococcal pneumonias that occurred after the age of 60.

3. Pneumococcus Type III pneumonia is relatively commoner in women than in men. The incidence rate for women is 18.2%, as compared with 11.6% for men. This is in sharp contrast to Type I and Type II infections, where the incidence per cent for the two latter types is considerably higher for males than for females.

4. Pneumococcus Type III pneumonia is very prone to occur in individuals who are already the victim of some chronic disease. In the present series of 500 cases, 49.9% of the patients were afflicted with some chronic malady. This association of chronic disease with pneumonia was much higher in Type III than in Type I or Type II infections.

5. Bacteremia was noted in 29.4% of the Type III patients who were subjected to blood cultures.

6. The death rate for the entire series of 500 cases of Type III pneumonia was 42.2%, a figure which agrees closely with that reported by other investigators. In Bellevue Hospital, however, Type III pneumonia ranks second in severity, being surpassed by pneumococcus Type II pneumonia with a death rate of 48.8%.

7. The death rate for Type III pneumonia was influenced by a number of factors. In bacteremic cases it was 85.4%. The death rate is much affected by age and the incidence of chronic systemic disease. In patients under 40 years the death rate was approximately 20%; over 60 years, 65.4%. In patients without systemic disease the death rate was 32.1%; with systemic disease, 53.6%.

8. There is no satisfactory serum therapy for pneumococcus Type III pneumonia at the present time. The most promising outlook with respect to a specific treatment for this infection is the

enzyme of Avery, which destroys the specific carbohydrate in the capsule of pneumococcus Type III, and which in the case of animals infected experimentally with lethal doses of Type III pneumococcus, has shown distinctly curative properties.

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STUDIES OF VITAMIN C EXCRETION AND SATURATION.*

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In 1933 Harris, Ray and Ward,[1] using Birch, Harris and Ray's[2] micromodification of Tillmans'[3] titration method for the determination of vitamin C found that normal human subjects excreted sig-

* Read in abstract at the meeting of the American Society for Clinical Investigation, Atlantic City, May 6, 1935.

nificant amounts of the vitamin in the urine.* The usual daily excretion was observed to be relatively constant (30 to 33 mg.). Well-nourished normal subjects were found to behave as though they had appreciable reserve "stores" of the vitamin, for when the vitamin was temporarily withheld from their diet they continued to excrete it for a time at an almost steady rate. When a large dose of the vitamin was given an increase in the urinary excretion was observed. These observations led them to believe that the urinary output was dependent both on the immediate intake and on the past nutritional history, that is to say, on the state of vitamin "saturation." In the same year von Eekelen, Emmerie, Josephy and Wolff[4] reported a series of "normal values" for 24-hour excretion similar to those of Harris, Ray and Ward.

Hess and Benjamin,[10] in 1934, studied the urinary excretion of the vitamin in children and were able to detect an appreciable excretion only when large amounts of vitamin C were fed. However, Harris and Ray[11] found the excretion of the vitamin by well-fed children to be of the same order as that of adults when expressed on a basis of body weight. Hess and Benjamin were led to conclude that the amount of vitamin C in the urine of children under normal dietary conditions is negligible, and when present in significant amounts represents an excess which appears after complete saturation of the tissues has occurred. We believe these conclusions are incorrect and that their subjects probably had a deficient store and a low intake of vitamin C. Rohmer, Sanders and Bezssonoff[12] found vitamin C in measurable quantities in the urine of infants. Infants of 5 months of age continued to excrete the vitamin when fed a diet low in vitamin C, but when older children were placed on a vitamin C-low diet the excretion of the vitamin fell to a low level.

Johnson and Zilva,[6] in 1934, studied the urinary excretion of vitamin C and were unable to find the relatively constant excretion observed by Harris, Ray and Ward.[1] They found that the usual daily output varied from 0 to 15 mg. in 3 subjects and from 80 to 150 mg. in the fourth. This variation was related to differences in the diets of the subjects tested. When average doses of 100 mg. daily were given to one subject on a low vitamin C diet, Johnson

* Although the substance reacting in urine with Tillmans' reduction indicator (2.6 dichlorophenol-indophenol) as the test is ordinarily performed has not been proven conclusively to be vitamin C (ascorbic acid), satisfactory evidence of its identity with the vitamin has been obtained through biologic assay by von Eekelen, Emmerie, Josephy and Wolff[5] and by Johnson and Zilva.[6] Recently Guerrant, Rasmussen and Dutcher[7] found that the amounts of vitamin C in fruit and vegetable juices as determined by the method of Tillmans compared closely with those determined by biologic assay. The specificity of the method for the determination of the vitamin in urine has also been investigated by Harris[8,9]. He concluded that no known constituent of urine was likely to interfere, provided the titration was carried out rapidly.

and Zilva found that no significant amounts were excreted in the urine until the 7th day. The output then gradually rose until the 17th day, after which it remained at a constant level of about 76% of the intake. They considered this subject saturated with vitamin C, and found that if now, after a lapse of 5 days, a dose of 180 mg. were given, 80% of it was returned in the urine. When unsaturated subjects were given larger doses they excreted about 60% by the 5th day, and maintained this level as long as the dose was continued. When the test dose was discontinued the urinary excretion of the vitamin quickly fell to the subject's usual level. Harris and Ray[11] similarly observed that when subjects on a vitamin C-free diet were given 140 mg. of vitamin C daily, there was very little increase in the urinary excretion of the vitamin. When 280 mg. of vitamin C were given daily the subject rapidly became saturated and after 6 days excreted 80% of the daily dose. When the administration of the vitamin was stopped, excretion quickly fell to a low level. Johnson and Zilva[6] concluded that there seemed to be "a definite capacity for 'saturation' which is independent of the dose" and Harris and Ray[11] that the state of saturation of the subject depends on the amount of vitamin C in the past diet.

Harris and Ray,[11] in their second paper, studied the excretion of vitamin C in a small group of children, some scorbutic, others presumably with a latent scurvy and the remainder normal. A few normal adults were also included. They found the children with scurvy to have very low excretions (0.4 to 0.7 mg. daily) and in them fairly large test doses of the vitamin failed to provoke any significant urinary excretion. After cure of the scurvy the daily excretion rose to 1.4 to 2.4 mg., and large test doses now produced a sharp rise in excretion. Subjects with latent scurvy and those with a definite history of dietary insufficiency also had fairly low excretions which suggested that such studies of urinary excretion might be of clinical value.

Early in 1935 Schroeder,[13] using a different method (iodometric titration), arrived at conclusions similar to those of Harris, Ray and Ward[1] and Johnson and Zilva[6] and found a normal daily excretion of 19 to 29 mg. Following test doses of 300 mg. of vitamin C there was a rise in the excretion of the vitamin.

Experimental. The purpose of our study was to determine the daily excretion and degree of "saturation" with vitamin C of subjects either patients of the clinic or persons of a similar social and economic class, whose diets were suspected of being deficient in various respects. For comparison a supposedly normal group made up of members of the staff was included. In addition we studied the excretion of vitamin C in 4 normal subjects over much longer periods and under varying conditions, with reference to the excretion of vitamin C following "saturation," the rate at which "sat-

uration" is lost and the effect of giving small amounts of vitamin C to subjects in the "saturated" and "non-saturated" states. Thirty-one subjects in all were studied, including 15 in the "patient" group, 9 members of the non-resident hospital staff and 7 members of the resident staff. All of the patients were ambulatory and at the time of the test were free of any significant complicating illness. In general, their diets were known to be low in protein, fresh fruits and milk. Though high in fresh vegetables, their habitual methods of cooking these in large quantities of fat for long periods of time may have lowered the initial vitamin C content. The non-resident hospital staff group was composed of doctors, technicians and clerical workers whose diets were in no way uniform. Some were known to take fairly large amounts of vitamin C-containing foods, while others took rather small amounts, due to dietary preferences and dislikes. The third group, members of the resident staff, all ate in the hospital dining rooms, and were offered the same food. The diet was presumably well balanced, and differed individually only as their personal tastes differed. The 4 subjects who were studied over a longer period were from the non-resident staff group. Though their diets were believed in the beginning to be adequate, it is possible that in 3 of them the daily intake of vitamin C was rather small. After a preliminary period on their usual diet these 4 subjects were placed on a vitamin C-"free" diet for the subsequent period of the experiment.

The vitamin C content of the urine was determined by the use of Tillmans'[3] indicator, 2.6 dichlorophenol-indophenol, standardized every 3 days against a known solution of ascorbic acid. The micro technique described by Harris and Ray was used with few exceptions. The indicator was titrated from a micro-burette into an aliquot of acidified urine and the amount of ascorbic acid expressed in milligrams. Titrations were carried out quickly and the volume of the aliquot of urine was varied inversely with the amount of ascorbic acid it was expected to contain. When possible, the specimens were titrated as soon as voided. When this was impractical, about 10% 2N sulphuric acid was used as a preservative. In all the tests of daily excretion 2 or more 24-hour determinations were carried out, and the figures for daily excretion represent an average of these determinations. Tests of "saturation" consisted in determining the per cent of a test dose (usually about 600 mg.) excreted in the urine in the 24 hours during which this amount was given. The coöperation of the subjects was excellent and we feel certain that all the urine was obtained. In all the experiments in which vitamin C was given, fresh orange juice was used as the source, the ascorbic acid content being determined by titration as described above. All of the experiments were carried out during the winter and early spring months.

Results. The results of the tests of daily excretion are shown in Table 1. In the patient group the daily excretion ranged from

TABLE 1.—THE DAILY (24 HOUR) URINARY EXCRETION OF VITAMIN C (ASCORBIC ACID).*

Patient group.		Resident staff.		Non-resident staff.	
Subject.	Vitamin C, mg.	Subject.	Vitamin C, mg.	Subject.	Vitamin C, mg.
F. G.	7.5	C. T.	12.2	H. F.	10.7
F. W.	9.0	R. B.	12.3	E. W.	14.9
H. K.	10.0	W. F.	12.9	J. A.	15.5
R. J.	12.0	R. T.	15.1	J. Y.	20.1
V. C.	13.0	A. W.	16.0	F. B.	22.3
L. F.	14.2	M. M.	23.3	A. B.	30.8
C. S.	15.0	M. G.	24.5	M. C.	43.0
W. J.	16.0			F. R.	64.2
C. J.	16.0			M. D.	80.1
K. S.	17.5				
E. M.	18.5				
A. R.	19.0				
A. J.	22.0				
J. N.	23.0				
H. S.	34.0				

* In each group the values are arranged in ascending order.

TABLE 2.—RETENTION AND EXCRETION OF TEST DOSE OF VITAMIN C (ASCORBIC ACID).

Subject.	Test dose, mg.	Excretion.		Apparent retention.	
		Mg.	%.	Mg.	%.
Patient group:					
F. W.	600	13.7	2.3	586.3	97.7
R. J.	493	15.8	3.2	477.2	96.8
H. K.	493	18.4	3.7	454.6	96.3
E. M.	784	32.5	4.1	751.5	95.9
J. N.	425	17.6	4.1	407.4	95.9
H. S.	637	31.3	4.9	605.7	95.1
C. S.	414	20.4	4.9	393.6	95.1
W. J.	417	22.9	5.5	394.1	95.5
L. F.	395	31.1	7.9	363.9	92.1
F. G.	636	56.4	8.9	579.6	91.1
C. J.	634	73.8	11.6	560.2	88.4
V. C.	654	88.2	13.5	565.8	86.5
A. R.	493	124.0	26.0	369.0	74.0
A. J.	493	172.0	34.9	321.0	65.1
Resident staff:					
A. W.	633	11.4	1.8	621.6	98.2
R. T.	594	20.5	3.5	573.5	96.5
C. T.	706	28.7	4.1	677.3	95.1
R. B.	706	38.2	5.4	667.8	94.6
W. F.	706	44.0	6.2	668.0	93.8
M. G.	654	223.0	32.3	468.0	67.7
M. M.	646	239.0	37.0	407.0	63.0
Non-resident staff:					
J. Y.	288.7	22.1	7.7	266.6	92.3
J. A.	420	64.1	15.3	355.9	84.7
H. F.	968	167.2	17.3	800.8	82.7
E. W.	586	207.0	35.3	379.0	64.7
M. D.	312	193.7	62.7	118.3	37.3
M. C.	352	240.0	68.2	112.0	31.8
F. R.	573	557.0	97.2	16.0	2.8

7.5 to 34 mg., 12 of the 15 subjects excreting less than 20 mg. Among the resident staff group the excretion varied between 12 and 24.5 mg., only 2 showing an excretion above 20 mg. Both of these subjects are dietitians. The non-resident staff group excreted from 5 to 80 mg. and 6 of the 9 showed an excretion of 20 mg. or more.

TABLE 3.—EXCRETION OF VITAMIN C AFTER SATURATION. SUBJECTS ON VITAMIN C-"FREE" DIET.

Subject.	Days.	Test dose, mg.	Excretion. Mg.	Excretion. %
M. C.	1	...	38.4	
	2	600	311.4	51.9
	3	600	539.0	89.9
	4	...	254.1	
	5	...	59.3	
	6	600	444.3	75.2
	7	...	57.6	
	8	...	36.8	
	9	...	38.5	
	10	...	34.0	
	11	...	21.4	
J. Y.	1	...	38.9	
	2	600	378.5	63.1
	3	600	382.8	64.8
	4	600	429.8	71.6
	5	600	596.2	99.4
	6	...	131.0	
	7	...	46.4	
	8	...	39.2	
	9	...	45.4	
	10	...	36.8	
	11	...	39.7	
	12	...	40.7	
	13	...	28.7	
	14	...	19.5	
J. A.	1	600	497.4	79.6
	2	600	581.0	96.8
	3	...	112.2	
	4	...	76.4	
	5	...	48.0	
	6	600	422.0	70.4
	7	600	586.8	97.8
	8	...	68.8	
H. F.	1	...	32.7	
	2	600	425.2	70.9
	3	600	367.0	61.2
	4	600	396.7	66.3
	5	600	211.3	35.2
	6	600	Lost specimen	
	7	600	556.0	94.3
	8	...	107.4	
	9	...	45.0	
	10	...	32.0	
	11	...	26.6	
	12	...	17.7	
	13	...	19.4	
	14	...	18.1	
	15	...	13.1	

The results of the saturation tests are shown in Table 2. In the patient group 2.3 to 34.9% of the test dose was excreted, or, more

significantly perhaps, 65.1 to 97.7% of the dose was apparently retained. Of the 15 subjects, 13 excreted a very small part of the amount given. All of them were subjects who had shown a low daily excretion. The one subject who had a fairly high daily excretion excreted a considerable part of the test dose. Among the resident staff group the excretion of the test dose varied from 1.8 to 37%. Only the 2 subjects with the higher daily excretion excreted more than 30% of the test dose. In the non-resident staff group the excretion of the test dose ranged from 7.6 to 97.2%. The majority of the subjects in this group excreted a considerable percentage of the test dose and had shown a relatively high daily excretion. Those who excreted smaller amounts of the test dose were the ones who had had a smaller daily excretion.

TABLE 4.—EXCRETION OF VITAMIN C AFTER SATURATION.
SUBJECTS ON USUAL DIET.

Subject.	Days	Test dose, mg.	Excretion.	
			Mg.	%
M. C.	1	...	45.3	
	2	352.6	240.1	68.2
	3	378.3	325.1	82.7
	4	...	146.4	
	5	...	186.8	
	6	...	88.6	
	7	...	72.0	
	8	...	82.8	
J. Y.	1	...	15.0	
	2	288.7	22.1	7.7
	3	420.0	146.1	34.8
	4	395.5	271.4	54.8
	5	691.0	579.0	84.0
	6			
	7	...	56.5	
	8	...	51.8	
	9	...	48.3	
J. A.	1	...	13.8	
	2	420.0	64.1	15.3
	3	592.5	533.6	90.0
	4	656.0	525.8	80.0
	5	...	82.5	
	6	...	62.8	
	7	...	39.4	
H. F.	1	600.0	258.0	43.0
	2	600.0	549.6	91.5
	3	...	38.9	
	4	...	32.7	
	5	600.0	425.2	70.9

Certain of the data obtained from the study of 4 subjects over a much longer period of time are shown in the remaining tables. When the subjects were maintained on a vitamin C-"free" diet following "saturation," the daily excretion was observed to fall rapidly to a low level (Table 3). Thus, Subject H. F., who excreted 556 mg. on the 6th and last day of "saturation," excreted 107.4 mg. on the 1st and 45 and 32 mg. on the 2d and 3d days thereafter, respectively. By the 8th day the excretion had fallen to 13.1 mg.,

an amount which was about equal to the daily excretion on her normal diet and comparable to that found in subjects suspected of an inadequate intake of the vitamin. All the subjects on a vitamin C-"free" diet showed a gradual but steady decrease in daily excretion at a rate which varied in the individual subjects but presumably would eventually have reduced excretion to subnormal levels in all the subjects, had the experiment continued long enough.

TABLE 5.—THE VITAMIN C EXCRETION OF "SATURATED" SUBJECTS, GIVEN AMOUNTS OF THE VITAMIN COMPARABLE TO THOSE TAKEN IN A GOOD DIET,* WHILE MAINTAINED ON A VITAMIN C-"FREE" DIET.
(Comparison With the Excretion of the Same Subjects After Saturation, While on Their Usual Diet.)

		Vitamin C-free diet.			Usual diet.		
		Vitamin C intake,	Vitamin C excretion.		Vitamin C intake,	Vitamin C excretion.	
Subject.	Days.	mg.	Mg.	%.	mg.	Mg.	%.
M. C.	1	1,000	389.8	39.0			
	2	1,000	539.1	53.9			
	3	930	841.1	90.2	352.6	240.1	68.2
	4	1,000	1,059.0	160.0	378.3	325.1	82.7
	5	..	222.0	...	...	146.4	
	6	75	72.0	96.4	...	186.8	
	7	75	85.2	113.5	...	88.6	
	8	75	86.9	115.8	...	72.0	
	9	50	...	...	...	82.8	
	10	75	82.0	109.4			
J. Y.	1	600	150.5	25.8			
	2	600	344.3	57.4	288.7	22.1	7.7
	3	600	586.4	98.1	420.0	146.1	34.8
	4	300	307.1	102.3	395.5	271.4	54.8
	5	1,000	878.8	87.9	691.0	579.0	84.0
	6	..	173.4				
	7	100	90.6	90.6	...	56.5	
	8	100	117.5	117.5	...	51.8	
	9	100	204.5	204.5	...	48.3	
	10	..	43.3				
	11	100	51.8	51.8			
	12	100	116.1	116.1			
H. F.	1	1,000	508.1	50.8			
	2	1,000	690.5	69.1			
	3	1,011	773.6	76.5			
	4	1,000	511.5	51.2			
	5	747.3	344.4	45.1	600.0	258.0	43.0
	6	1,000	941.8	94.2	600.0	549.6	91.5
	7	50	151.4	303.0	...	38.9	
	8	50	116.3	232.4	...	32.7	
	9	50	58.6	117.7			
	10	50	80.6	160.9			
	11	50	71.9	143.6			
	12	76					
	13	50	53.9	107.8			

* These subjects were kept on an otherwise vitamin C-free diet.

With the subjects on their usual diet, the decrease in daily excretion after "saturation" corresponds roughly to the nature of the individual diets. In those subjects whose usual diet contained a considerable amount of vitamin C, the decrease, though rapid, was

not as great as when on the vitamin C-"free" diet. Thus, Subject M. C. on his usual diet excreted 82.8 mg. on the 5th day following "saturation" (Table 4). During a similar test when on a vitamin C-"free" diet, the excretion on the 5th day was 21.4 mg. (Table 3). Subject J. Y., whose usual diet was believed to be rather low in

TABLE 6.—RESATURATION TESTS WITH VITAMIN C AT VARYING INTERVALS. SUBJECTS ON VITAMIN C-"FREE" DIET.

Subject.	Days.	Test dose, mg.	Excretion.	
			Mg.	%.
M. C.	1	600	378.6	63.1
	2	600	517.2	86.2
	3	...	156.5	
	4	...	65.2	
	5			
	6			
	7			
	8	...	42.3	
	9	...	38.4	
	10	600	311.4	51.9
	11	600	509.3	84.8
	12	...	143.5	
	13	...	53.2	
	14	...	30.3	
	15	600	293.1	48.8
	16	600	392.2	65.4
	17	600	539.0	89.9
	18	...	254.1	
	19	...	59.3	
	20	600	444.3	75.2
J. Y.	1	600	120.2	20.3
	2	600	469.9	78.3
	3	600	474.9	79.1
	4	600	542.6	90.5
	5	...	123.3	
	6	...	77.1	
	7	...	33.9	
	8	...	38.8	
	9	600	378.5	63.0
	10	600	382.8	64.8
	11	600	429.8	71.6
	12	600	596.2	99.4
J. A.	1	600	587.3	97.9
	2	600	594.3	99.1
	3	600	625.5	104.2
	4	600	621.7	103.6
	5	600	582.7	97.2
	6	600	586.1	97.7
	7	600	477.4	79.6
	8	600	581.0	96.8
	9	...	112.2	
	10	...	76.4	
	11	...	74.9	
	12	600	422.5	70.4
	13	600	586.0	97.8

vitamin C, when on that diet excreted 48.3 mg. on the 4th day. When on a vitamin C-"free" diet after "saturation," the excretion on the 4th day was 45.4 mg. (Tables 3 and 4).

When known amounts of vitamin C, comparable to those which

might be taken in a "good" diet (50 to 100 mg.), were given to the subjects on a vitamin C-"free" diet following "saturation," the daily excretion was not only greater than when no vitamin was given but was higher than when the subject was continued on his usual diet.

"Resaturation" tests at varying intervals showed that "saturation" is quickly lost when the individual is on a vitamin C-"free" diet (Table 6). In as short a time as 2 days "saturation" may be lost and a "resaturation" test may show as much as 25% retention of the test dose (Subject M. C.). Some subjects even on their usual diet appear to lose their "saturation" quickly (Table 4). When, however, 50 to 100 mg. per day were given following "saturation," the "saturation" was apparently maintained for some time (Table 5).

TABLE 7.—EXCRETION OF VITAMIN C BY UNSATURATED SUBJECTS DURING ADMINISTRATION OF SMALL, VARYING AMOUNTS OF VITAMIN C. SUBJECTS ON VITAMIN C-"FREE" DIET.

Subject.	Days.	Test dose, mg.	Excretion, mg.
M. C.	1	...	36.8
	2	...	38.5
	3	...	34.0
	4	...	21.4
	5	...	32.8
	6	...	39.4
	7	25	32.6
	8	50	36.3
	9	100	39.8
J. Y.	1	...	28.7
	2	...	19.5
	3	...	31.5
	4	...	27.2
	5	...	24.5
	6	25	25.3
	7	50	24.9
	8	75	25.5

The intake of small but varying amounts of vitamin C (25 to 100 mg.) by "unsaturated" subjects on a vitamin C-"free" diet did not affect the daily excretion significantly (Table 7). Thus Subject J. Y., whose daily excretion for 5 days preceding the test ranged from 19.5 to 31.5 mg., excreted 24.9 to 25.5 mg. daily during the 3 days on which he was given 25, 50 and 75 mg., respectively. In contrast, in the saturated state, the administration of 100 mg. was immediately reflected in the urinary excretion (Table 5).

When comparison is made between the amounts of vitamin C excreted following nearly complete saturation (with the subject on a vitamin C-"free" diet) and the amounts retained at the next subsequent saturation, a considerable discrepancy is found and the amounts which were required to "resaturate" are found to be considerably greater than the amounts which had been excreted in the interval (Table 8). In nearly every period of this kind in which suitable data were available, this discrepancy was observed. Dif-

TABLE 8.—COMPARISON BETWEEN THE AMOUNTS OF VITAMIN C EXCRETED FOLLOWING NEARLY COMPLETE SATURATION AND THE AMOUNTS RETAINED AT THE NEXT SUBSEQUENT SATURATION. SUBJECTS ON VITAMIN C-"FREE" DIET.

Subject.	Days.	Vitamin C intake, mg.	Vitamin C excretion in urine, mg.	Apparent retention, mg.		
M. C.	1	600	311.4			
	2	600	509.3			
	3	...	143.5			
	4	...	53.2		Total excretion (urine)	227.0 mg.
	5	...	30.3			
	6	600	293.1	306.9		
	7	600	392.2	207.8	Total apparent retention	575.7 mg.
	8	600	539.0	61.0		
					Unaccounted for in urine	348.7 mg.
H. F.	1	600	556.0			
	2	...	107.4			
	3	...	45.6			
	4	...	32.2			
	5	...	26.6		Total excretion (urine)	294.7 mg.
	6	...	17.7			
	7	...	19.5			
	8	...	18.0			
	9	...	13.1			
	10	...	14.7			
	11	1,000	508.1	492.0		
	12	1,000	690.5	309.5		
	13	1,010.8	773.6	237.2	Total apparent retention	1,988.3 mg.
	14	1,000	511.5	488.5		
	15	747.3	344.4	402.9		
	16	1,000	941.8	58.2		
					Unaccounted for in urine	1,693.6 mg.
J. Y.	1	600	542.6			
	2	...	123.3			
	3	...	77.1		Total excretion (urine)	273.2 mg.
	4	...	33.9			
(First period)	5	...	38.9			
	6	600	378.5	221.5		
	7	600	387.8	217.2	Total apparent retention	612.7 mg.
	8	600	429.8	170.2		
	9	600	596.2	3.8		
					Unaccounted for in urine	339.5 mg.
	1	600	596.2			
	2	...	131.0			
	3	...	46.4			
	4	...	39.2			
	5	...	45.4			
	6	...	36.8			
	7	...	39.7			
	8	...	40.7		Total excretion (urine)	540.6 mg.
(Second	9	...	28.7			
period)	10	...	19.5			
	11	...	31.5			
	12	...	30.0			
	13	...	27.2			
	14	...	24.5			
	15	25	25.3			
	16	50	24.9	25.1		
	17	75	25.5	49.5	Total apparent retention	793.4 mg.
	18	600	150.5	449.5		
	19	600	344.3	255.7		
	20	600	586.4	13.6		
					Unaccounted for in urine	252.8 mg.

ferences in the amount of the vitamin unaccounted for in the urine were found among the different subjects and in the same subject at different times. When the amounts are computed on a daily basis the same differences are found.

Discussion. Although the values for the daily excretion vary widely, they correspond to the probable differences in vitamin C intake of the different groups and the individual subjects. Thus, the lowest values generally were found among the patient group whose diets as a group were undoubtedly lowest in vitamin C. Even the surprisingly low excretion of most of the resident staff group seems adequately explained by a dietary preference which limited the intake of vitamin C-containing foods in spite of the provision of an adequate diet. Individual variations are similarly explained. For example, the 2 subjects with the highest excretions in the non-resident staff group were found to be taking unusually large amounts of the vitamin.

Any conclusions regarding the "normal" daily excretion are made difficult by the lack of knowledge of the effect and manifestations of a slight deficiency of vitamin C and ignorance as to the optimal intake. The results of other investigators show an even wider range than ours, from 0 to 150 mg. (Johnson and Zilva). There is reason to believe, however, that in some of the studies reported, the diets of the subjects showing the low daily excretions were to some degree deficient.[6,10] In our study, the patient group, most of whom had a small excretion, were drawn from a class in whom manifestations of a mild scurvy have been observed and a few of the subjects themselves had had suspicious symptoms in the past. Disregarding those in the supposedly normal group whose diet was found to be questionable and taking those whose diets appeared reasonably adequate, the daily excretion of vitamin C was found to be in the neighborhood of 20 to 80 mg., values which correspond fairly well to those of Harris and Ray. On this basis we have tentatively adopted an excretion of 20 mg. per day as the lower normal limit of excretion in adults.

Some additional evidence respecting the normal daily excretion is obtained from the extended study of the 4 normal subjects. When amounts of vitamin C which roughly correspond to those taken in a "good" diet were given to nearly "saturated" subjects on a vitamin C-"free" diet, the daily excretion was maintained at a level somewhat above the general level of the subjects on the "better" diets and at a higher level than these same subjects excreted in an "unsaturated" state on their usual diet.

The results of the "saturation" tests show the same relationship to the probable intake of vitamin C as do the tests of daily excretion, and correspond roughly to the latter. It should be emphasized that "saturation" (80 to 100% of a test dose) in all probability

does not reflect an optimum or normal store of vitamin C in the body but is an artificial state which can be created only by the intake of excessive amounts of the vitamin. This conclusion is supported by the rapidity with which such a state is lost when the intake of large amounts is stopped (Table 3), as well as by the fact that only one subject in the group whose diets were considered to be adequate had an excretion even approaching 80% of the test dose. With our present knowledge it is impossible to define the normal degree of "saturation." While it is unlikely that the normal state is represented by an excretion of 80 to 100% of a test dose (about 600 mg. in adults), it seems probable that a return as low as 20% or less of such an amount reflects a suboptimal store of vitamin C. An excretion less than 20% (usually much less) of such a test dose was found in nearly all of the patient group and in several others whose diets were found to be at least questionably inadequate and whose daily excretion was low. Among those whose diets were considered reasonably adequate and who had the higher daily excretions, usually more than 30% of the test dose was excreted. For these reasons it is tenatively concluded that under normal conditions at least 30% of the test dose of the size we have used should be excreted. The fact that a few subjects whose daily excretion was above 20 mg. excreted less than 30% of the test dose may mean that a "normal" excretion may be maintained in the presence of an inadequate store.

The very great and abrupt reduction in daily excretion in a "saturated" subject when the intake of the vitamin is stopped (Table 3) suggests that the urinary excretion is regulated by the daily metabolism and is not merely an indication of an excess of the vitamin, as suggested by Hess and Benjamin.[10] Rather there appears to be a true storage with the controlled release of such amounts as are needed. There is some indication from our results that, in the absence of continued ingestion of vitamin C, this daily excretion, and presumably the amount used daily, gradually lessens as the store decreases until finally with the depletion of the reserve and the onset of scurvy the excretion becomes negligible. It cannot as yet be determined to what extent the rate at which daily excretion decreases depends on differences in the amount of vitamin required (or used). The fact that some vitamin continues to be excreted in spite of a dwindling reserve suggests that a circulating supply is maintained as long as possible, a certain amount of which is lost through kidneys which have no threshold for the excretion of this substance. If such an explanation is correct, the daily excretion is a true index of the amount of the vitamin which is being used by the body and of the adequacy of the supply, provided that the daily excretion is not sufficiently affected by other factors as to create a false impression. Two such possible factors are varia-

tions in the amount metabolized daily and in the daily intake. It is true that successive determinations may show variations in output with the subjects on their customary diet. However, in our experience these variations rarely exceed a few milligrams and the values of the daily excretion follow closely the usual trend of the individual subject. Also according to our results it seems unlikely that these variations are due to differences in intake, if the latter are in the neighborhood of amounts which might be contained in an ordinary diet and if the individual is not saturated or nearly saturated (Table 7). It appears that in the unsaturated subject any amount beyond that which may be needed for immediate use is stored and does not affect the daily excretion. Therefore, the daily fluctuations which are observed are probably the result of metabolic or similar factors and do not affect the value of the daily excretion as an index of the amount of vitamin C stored and used by the body.

Evidence of destruction of vitamin C within the body or its excretion by other channels is found in the discrepancy between the amount which is retained on a resaturation and the amount excreted in the urine in the period following the previous saturation (Table 8). In most instances the amount retained on a resaturation was considerably greater than that which had been lost in the urine following the previous saturation. At the present time no information is available as to the fate of this unaccounted-for portion. In the absence of other channels of excretion, variations in this fraction may be related to differences in requirements of different individuals or to variations in the same individual under different conditions.

Summary and Conclusions. Of 15 subjects whose diets were suspected of being inadequate in vitamin C, 12 excreted less than 20 mg. of the vitamin in the urine daily. Of 16 normal control subjects whose diets supposedly were adequate, 8 also excreted less than 20 mg. In the latter group subsequent inquiry suggested a limited intake, for one or another reason, of vitamin C among those with the low daily excretions.

Of the 31 subjects, 21 excreted but a very small part of a large test dose of the vitamin in the 24 hours during which it was administered, indicating an apparent retention of a large amount and suggesting a small store in the body. In general the tests of "saturation" corresponded to the tests of daily excretion and the probable dietary intake of the vitamin.

In 4 normal subjects it was found that: (1) Following "saturation" the urinary excretion of vitamin C quickly fell to a low level when the subject was kept on a vitamin C-"free" diet. On the "usual" diet the fall was nearly as great and as rapid.

2. With the subjects on their usual diet or a vitamin C-"free" diet, "saturation" was quickly lost when the administration of

vitamin C was stopped, "resaturation" tests at intervals of 2 to 3 days showing an apparent retention of as much as 25% of a test dose.

3. The administration of small but varied (25 to 100 mg.) doses of vitamin C to "unsaturated" subjects had little effect on the daily urinary excretion.

4. With the subjects on a vitamin C-"free" diet, the amount of the vitamin excreted in the urine in any given period following "saturation" is usually much less than the amount required to "resaturate."

5. For the present, a daily urinary excretion of vitamin C of 20 mg. and an excretion of 30% of a test dose (about 600 mg. in adults) is suggested as the lower limits of normal daily excretion and of "saturation" respectively.

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CLINICAL OBSERVATIONS ON PULMONARY BLOOD FLOW IN SILICOSIS AND OTHER FIBROTIC CONDITIONS OF THE LUNGS.*

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Connective tissue proliferation assumes a predominant rôle in many pulmonary diseases, and yet in the presence of such extensive anatomic changes the physiologic processes of the lungs often appear to go on practically unimpaired. This seems to us attributable to, at least, two important circumstances: (1) The velocity of blood flow in the lungs remains normal, and (2) the function of the alveolar capillary wall is practically undisturbed. In a sense, therefore, the widespread fibrosis of silicosis or of tuberculosis, lues or carcinoma represents an extravascular condition of the lungs and, with notable exceptions, does not assail the capillary alveolar bed. In silicosis, as we shall see, fibrosis from the start is diffuse and throughout the capillary alveolar bed, reaching the parenchyma only later.

In this report we shall deal with studies in pulmonary blood flow in silicosis and in other pulmonary fibrotic states, describing methods and discussing briefly the type of fibrosis encountered and recording our results on blood velocity. Other aspects, among them studies in blood gases, will be left for a later publication.

Methods. We employed two procedures: (*a*) The crude pulmonary circulation time,[1] or the arm to tongue circulation time devised by Winternitz, Deutsch and Brüll,[2] who utilized the bitter tasting property of sodium dehydrocholate (decholin) (first employed by Neubauer[3]) for measuring the arrival of its bitter taste after intravenous administration. Fishberg, Hitzig and King[4] later substituted glusid (saccharin) for decholin. In healthy individuals the average time for the completion of the pulmonary circuit is about 16 to 18 seconds, covering the pulmonary arterial and pulmonary venous channels.

(*b*) As an adjunct to the above the ether time method was also utilized.[5,6] This represents the time consumed for the odor of ether (3 cc. of 10% ether in normal saline solution) to reach the breath after its introduction into an elbow vein. The average time in healthy individuals for the completion of this pulmonary arterial circuit is about 5 to 9 seconds. Subtracting this result from the larger figure, *i. e.*, 16 to 18 seconds, for the entire pulmonary circuit we obtain a difference of about 8 to 10 seconds and this may be accepted as a fairly reliable measurement in time of the velocity of blood in the pulmonary venous circuit.

At the outset we must state that the saccharin or taste time and the ether or odor time were normal in practically all conditions and circumstances of pulmonary disease with the following notable

* Presented before the VII^me^ Congres International des Accidents et des Maladies du Travail, Brussels, July, 1935.

exceptions: (*a*) When congestive heart failure was an accompanying or concomitant manifestation; (*b*) when myxedema was present, as after thyroidectomy for the relief of congestive failure (here the pulmonary circulation in both the arterial and venous system was slowed even after congestive failure had apparently subsided); (*c*) and in cases where we had good clinical ground for postulating the existence of pulmonary hypertension associated either with mitral valve disease or advanced emphysema; (here the ether time in some instances was prolonged to 12 to 18 seconds). A study of these latter cases will form the subject of a future communication in which observations on blood gas analysis correlated with probable derangements of the function of the alveolar membrane will be set forth. In passing, however, we may indicate at this point that we have reason to believe that increased ether figures represent an alteration in the membrane's capacity to diffuse gases through the alveolar membrane and are not due to any interference with the velocity in the pulmonary arterial circuit.

Retardation in blood velocity was confined primarily, if not wholly, to the pulmonary venous vessels and went hand in hand with congestive heart failure. In other words, *congestive heart failure is a phenomenon of disturbance of blood velocity, occurring primarily and from the very beginning in the venous system of the lungs.**

Fibrosis of the Lungs. With these tests many fibrotic pulmonary conditions were studied. Generally speaking, the fibrotic process in tuberculosis, lues, carcinoma, chronic infections, etc., presents scattered patchy connective tissue proliferations as a reactive response to the etiologic process in the areas affected. The changes take place throughout the parenchyma and secondarily extend to the pleura, mediastinum, diaphragm, etc.; the process is not centrifugal, the vast capillary alveolar bed remaining untouched essentially.

Thus, in tuberculosis neutrophils appear early in the formation of the tubercle and disappear at the stage of caseation, mononuclear and lymphocytic cells then taking over the phagocytosis of the débris. Fibrosis develops around the tubercle and also around cavities, but the fibrotic process fails to encroach upon the alveolar bed as a whole, however much it may involve isolated patches of alveoli. There are also some gross differences in the type of fibrosis seen here, as contrasted with silicosis; for example, the characteristic broad fibrotic apical and basal bands seen in tuberculosis and their tendency to be lateral and oblique as against the fibrotic strands in silicosis more longitudinal in direction and often characteristically

* On this point and related matters see: Miller, H. R.: The Rôle of the Lesser Circulation in Diseases of the Heart and Lungs, read December 7, 1934, at the Fiftieth Anniversary of the Founding of the Montefiore Hospital, New York City. See also: Hitzig, W. M., King, F. H., and Fishberg, A. M.: Arch. Int. Med., **55**, 112, 1935.

"tenting" the diaphragm. This brief description of fibrosis in tuberculosis holds also for syphilis and for carcinoma,* although in syphilis a greater production of perivascular fibrosis occurs as a consequence of the specific vascular-wall necrosis associated with this disease. In advanced and widely spread pulmonary tuberculosis the pulmonary blood velocity remained normal.

TABLE 1.—TUBERCULOSIS. NORMAL PULMONARY BLOOD VELOCITY IN 10 CASES OF ADVANCED PHTHISIS (SPUTUM POSITIVE) (FROM THE SEA VIEW HOSPITAL.)

Name.	No.	Age.	I. Ether time: velocity in pulm. arterial circuit. Seconds.	II. Saccharin time: velocity in entire(crude) pulm. circulation. Seconds.	III. Difference between II and I: velocity in pulm. venous circuit. Seconds.
T. G. . .	10202	67	5.00	15.5	10.50
H. L. . .	5161	38	7.00	12.5	5.50
S. G. . .	4949	59	6.50	17.0	10.50
C. M. . .	11512	43	7.25	14.0	6.75
G. F. . .	11676	58	6.00	13.5	7.50
S. G. . .	11760	32	5.50	16.0	10.50
M. N. . .	5866	60	6.00	15.0	9.00
W. Mc. .	4930	46	5.50	16.0	10.50
G. R. . .	8114	44	7.50	15.0	7.50
N. M. . .	9893	59	7.00	13.5	6.50

Quite different is the diffuse or centrifugal type of fibrosis involving the extensive alveolar capillary bed but leaving the parenchyma practically free; this is seen in extensive emphysema (primary or secondary), also in silicosis where the fibrotic thickening assails the fine lymphatic channels in the early stages and only much later and after prolonged silica exposure produces massive parenchymal alterations as well.

Silicosis, *par excellence*, is a fibrotic process. In the early stage phagocytosis is prominent, but even here connective tissue proliferation is to the fore early and continues long after the phagocytic activity subsides. Fibrotic thickening in the lymphatic channels ensues, the so-called perilymphatic nodulation appears at points of lymphatic vessel bifurcation and also where the lymphatics are crossed by bloodvessels or bronchial branches; the draining lymph nodes enlarge, mainly, the tracheobronchial group.

Up to this stage of perilymphatic nodulation restitution to normal is still possible, if no further exposure to silica dust takes place, and the stasis of silica dust and dust-laden phagocytes can leave the lymphatic channels free and clear.[7,8,9] The patient, in all probability, will then escape the further advances of the silica process, and from the point of view of compensation and insurance his condition will not be considered compensable.

* The table of figures in pulmonary carcinoma, for the sake of brevity, has been omitted; the results were within normal limits. No cases of pulmonary lues came to our attention.

With increased or continued exposure, however, to silica dust, perilymphatic nodulation, namely fibrosis and beading, will grow more marked. These beadings are the pseudotubercles of Mavrogordato (1922), the intralymphatic plaques of Carlton[10] (1924), and they are readily recognized in the Roentgen ray film. The lung parenchyma is not involved at this time, the lymphatic channels bearing the brunt of the change and exhibiting fibrotic thickening; this stage of the disease has been aptly termed by Mavrogordato "lymphatic cirrhosis." From the point of view of compensation in law, etc., these linear lymphatic thickenings and beading are looked upon as proof of pneumoconiosis, although the interparenchymatous lesions, *i. e.*, nodules, regarded as specific for silicosis, are not yet in existence. (According to Watkins-Pitchford,[11] the silicotic lesion is recognized in law only when it is visible and *palpable* in the lungs.) Under prolonged silica exposure these specific nodules eventually appear; they arise in the interstitial tissues of the parenchyma and not always or necessarily in relation to lymphatic tissues already involved. Occurring singly they may remain at about 1 mm. in diameter or else large massive induration takes place at the expense of the lung parenchyma; these parenchymatous lesions consist of dense connective tissue growth and are singularly free of cell elements.

Part and parcel of the silicosis picture is the frequent extensive emphysema surrounding areas of parenchymatous lesions and often forming characteristic cushions of emphysema at the apex and subapical regions; quite characteristic also is the occurrence of fibrotic strands or adhesions often touching the pleura, mediastinum and diaphragm; the interlobar fissures may also show some degree of thickening. Restitution to normal in this advanced state is, of course, beyond hope and any likelihood for clinical recovery extremely remote and even totally unexpected. The outlook is worse if tuberculosis should intervene. The superimposed tuberculosis leads to cavitation, further fibrosis and to destruction of those zones of the normal parenchyma tissues wedged in between the silicotic nodular masses and the periphery of the lungs.

On the behavior of pulmonary blood flow in the early stages of silicosis, up to and including the stage of perilymphatic nodulation, we have no data as yet, but in the advanced stages of silicosis with or without extensive tuberculosis our results demonstrate that the pulmonary blood velocity is normal both in the arterial and venous pulmonary circuits. This is particularly interesting in view of the fact that the process from the beginning is diffuse and peripheral and lasts for years.

Since pulmonary blood flow is retarded, practically speaking, only with the advent of congestive failure, these circulatory tests offer a simple practical means of detecting cardiac failure among silicotics

where right ventricular hypertrophy and its terminal lethal failure are not rare. The right heart enlargement and its final picture of congestive failure resemble in all features the similar pictures associated with other chronic pulmonary conditions (*cor pulmonale*). The application of these tests in silicosis discloses that the extensive and profound fibrotic alterations, with diffuse pericapillary and perilymphatic involvement cause no derangement of pulmonary blood flow.

TABLE 2.—SILICOSIS. NORMAL PULMONARY BLOOD VELOCITY IN 10 CASES OF ADVANCED SILICOSIS, 5 OF THESE CASES ALSO HAVING ADVANCED PHTHISIS. (FROM THE SEA VIEW HOSPITAL.)

Name.	No.	Age.	Silicosis.	TB.	Ether time: velocity in pulm. *arterial* circuit. Seconds.	Saccharin time: velocity in entire (crude) pulm. circulation. Seconds.	Difference between II and I: velocity in pulm. *venous* circuit. Seconds.
M. S.	922–28	53.0	+	0	7.5	12.5	5.0
E. D.	11315–35	43.0	+	0	6.0	14.5	8.5
J. H.	10989–34	65.5	+	0	6.0	18.0	12.0
F. C.	6711–32	45.0	+	0	5.5	16.0	10.5
V. S.	9042–33	57.0	+	0	5.5	14.0	9.5
M. S.	11413–35	30.0	+	+	5.0	14.0	9.0
W. G.	10926–34	54.0	+	+	8.0	17.5	9.5
V. S.	11064–34	55.0	+	+	5.0	13.0	8.0
H. K.	11555–35	35.0	+	+	5.0	13.0	8.0
J. S.	11335–35	54.0	+	+	6.0	15.0	9.0

Similarly, peripheral and diffuse (centrifugal) in distribution is the fibrotic process observed in conditions associated with excessive and persistent elevation of the pulmonary blood pressure, as, for example, in chronic mitral stenosis, in advanced emphysema, in a block of the lesser circulation by external pressure. The pathologic change is chiefly in the arteriocapillary bed, although in many cases the alterations include elastic fiber hypertrophy running through the walls of the entire pulmonary vascular tree. These latter changes particularly are the result of pulmonary hypertension and blood velocity plays no part.

The separation of the effects of pressure from those of velocity is readily observed in the larger vascular system. Thus, it is almost commonplace among hypertensives with marked elevation in blood pressure to find no disturbance in the rate of blood flow unless heart failure supervenes. The lesser circulation appears to be no exception to this general rule, and this is illustrated by our results of normal blood flow figures in cases of mitral disease* tested while free of congestive failure and in advanced emphysema* patients also free of congestive failure.

In emphysema the responsibility for pulmonary hypertension has been placed upon the misshaped or enlarged alveoli which are

* These tables have been omitted at this time and will be published in a future communication.

supposed to exert compression upon their adjacent capillaries. This conception, advanced by Cloetta,[12] if valid, confirms our belief based upon our own blood velocity figures and the antecedent results of Weiss and Blumgart,[13] that pulmonary hypertension and the rate of pulmonary blood flow are independent processes.

Summary. 1. The fibrosis in pulmonary disease assumes two main forms: (*a*) A diffuse type involving the vast capillary alveolar bed, associated, as a rule, with pulmonary hypertension and observed in emphysema or in obstruction to the lesser circulation (mitral stenosis, kyphoscoliosis, etc.), and (*b*) a circumscribed or "patchy" fibrosis involving the parenchyma and encountered in tuberculosis, carcinoma, etc. In silicosis the diffuse type is present early and the second, or patchy, form appears much later.

2. From a vascular point of view the heart and lungs are one organ; the lungs represent an enormous vascular sponge of ramified vessels stemming from the heart and surrounded by air sacs through which gases are exchanged between the circulation and the outside atmosphere. With this concept in mind it is not surprising to find that pulmonary disease and conditions associated with marked fibrosis remain extravascular, as a rule, and that when the peripheral vascular lung bed becomes involved a concomitant state of pulmonary hypertension is the rule. The heart, if at all affected, is drawn into the picture secondarily, either (*a*) by developing hypertrophy of the right ventricle as a response to this hypertension, in some cases accompanied by the terminal picture of so-called right heart failure; or else (*b*) the heart responds by altering its volume output as a compensatory reaction to an increase in the $A-V$ difference, this difference following as a result of an interference in gas exchange through a pathologically altered alveolar wall.

3. Unless cardiac failure (congestive failure) intervenes, the rate of pulmonary blood flow remains normal in both arterial and venous circuits in all pulmonary fibrotic conditions. To this there are few exceptions. As in other fibrotic conditions, the rate of pulmonary blood flow in silicosis is not deranged unless heart failure sets in.

4. The rate of pulmonary blood flow is retarded in the venous channels in the presence of cardiac congestive failure.

5. In a few instances of pulmonary fibrotic states the velocity of blood flow was retarded in the pulmonary arterial channels. Here the fault would appear to be in the alveolar membrane.

Thanks are due Drs. Ornstein, Reisner and Pine for permission and help in studying the patients from Sea View Hospital, and to Drs. Furman and Medoff, of the Montefiore Hospital Staff.

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MUMPS ORCHITIS.

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The main importance of the occurrence of orchitis in mumps is the possibility of atrophy with subsequent sterility and impotence. Sterility is, of course, lack of sex cells, while impotence[1] refers to the inability to perform the sex act. There are a number of causes for each, but the two are frequently confused. Other symptoms, to be further discussed, complicating the orchitis, may become very serious.

Historically, mumps is an ancient disease. Protalongo[2] was the first to recognize its contagious nature. As in most present-day texts, the disease is considered in a work on Epidemiology and Public Health published in 1922 by Vaughan.[3] Hippocrates was the first to mention testicular involvement, as seen by the following concise description from Vaughan:[4] "Some again, after a while, had painful phlegmons upon the testicles, sometimes upon one, sometimes upon both. Some had fevers, others none; most of them trouble and fatigue enough; but with respect to the chirurgical part they did very well." Hamilton, in 1752, recognized testicular atrophy as a possibility.[5] American army officers reported camp epidemics during the World War.[10, 11] The paper of Wesselhoeft,[12] published in 1920, is the most complete and up-to-date résumé on

mumps orchitis, although other statistics have been added later.[13] Since Hippocrates, orchitis has been recognized by nearly everyone, but especially since the nineteenth century, as a definite and serious complication.

For this study the case records of two Philadelphia hospitals are cited in an attempt to check on certain data found in the literature. Fourteen cases were all that could be found on file at the Hospital of the University of Pennsylvania;[14] 269 cases had been admitted to the Philadelphia Hospital for Contagious Diseases from 1918 through 1933.[15]

Though contagious, mumps is a relatively mild infection. The age incidence varies greatly; some writers[16] limit the disease to childhood while others[16, 17] note its occurrence in both children and adolescents. In the cases at the Philadelphia Municipal Hospital[15] there were two definite and distinct peaks: one in childhood, and the other in adolescence (Fig. 1). There has been a seasonal variation in incidence—according to some,[18] more cases are seen in the winter and spring, while other sources place the peak from November through February.[13] The sexes are equally susceptible[3, 18] and the actual figures in the Municipal Hospital cases were males 144 and females 125. Negroes seem more susceptible to mumps than whites, as shown by army statistics, where the morbidity was three times as great in the colored troops. The reverse was true in the Municipal Hospital cases—7 to 1 in favor of the whites. The higher proportion of cases in colored patients coming from the rural districts where there are more susceptibles and fewer immunes argues for the presence of a definite immunity from one attack, according to some writers. This immunity is generally undisputed,[3, 10, 15, 19, 20, 21] though some[10] consider it very fleeting. The injection experiments of Hess[22] and Gradwohl *et al.*[23] give further evidence of immunity production. Second attacks are mentioned in the literature[11, 24] and were recorded in both the hospitals series used for this paper.[14, 15] The degree of exposure and the acquired immunity are the determining factors in group and community incidence.[18, 86] To these must be added as further factors: general health, crowding, and the occurrence of carriers.[13] Contact is held indispensable to spread.

Transmission experiments[21, 25] have indicated that mumps is a virus disease; Rivers[26] says, "the evidence, however, that mumps is caused by a virus is suggestive enough to warrant its inclusion in a discussion of virus disorders." Other theories of causation include: salivary retention,[27] rheumatismal factors,[28] a micrococcus,[29, 30, 31] a diplococcus,[32, 33] a diplobacillus,[34] and recently a specific spirochete[35] in association with a small Gram-negative bacillus.[30] The portal of entry of the virus is obscure, although it is probably the upper respiratory tract.

Most writers agree on an incubation period of about 18 days. The mode of onset varies greatly, though malaise, slight fever, and tenderness at the angles of the jaw is the commonest sequence of events. Later, there is usually swelling of the parotids, a sensation of heat, limitation in the opening of the jaw, with headache and

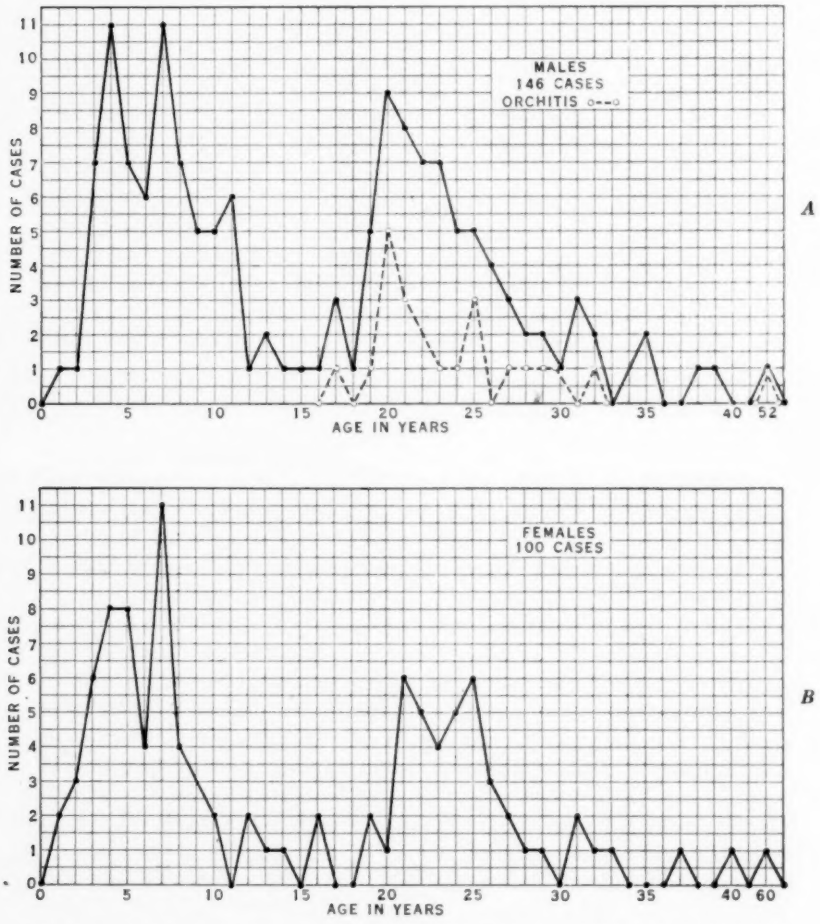

FIG. 1.—Age incidence of mumps and its orchitis: 246 cases—Philadelphia Hospital for Contagious Diseases.

earache. There is always a leukocytosis, principally neutrophils. Other findings compatible with a febrile state result, but the fever is often very slight. There may be gastro-intestinal symptoms. Rivers says, "During the course of mumps in an occasional patient, symptoms and signs referable to the central nervous system develop."

Involvement of the seventh and eighth nerves has been noted.[36, 37, 38] This is rare in uncomplicated cases. Suppuration never occurs in true mumps. The salivary glands and cervical lymph nodes may be affected.

The description of Hippocrates[32] gives a good picture of the malady: "Swellings appear near the ears, in many cases on one side, in most on both, without a fever or any confinement, but in some with a little fever. In all, they disappear without either inconvenience or suppuration, contrary to the custom of such tumors from other causes. At this particular time, they were naturally soft, large, diffused, without inflammation or pain, and went off universally without any visible signs. Children, young persons, adults, especially those who frequented the public places of exercise, were most subject to them. A few women were also affected. The greatest part had dry coughs, which were soon succeeded by hoarseness."

Etiology and Pathogenesis. The etiologic agent responsible for the testicular affection is the same as that of mumps.[8, 39] Just how orchitis occurs has never been adequately settled, though a number of theories have been advanced.

Before enumerating these, the quite definite relation between the parotids and genitalia should be briefly considered. Paget[40] mentions that occasionally affections of the breasts and labia after mumps in women point to some special connection between the salivary glands and the genital organs. He also mentions the enlargement of the salivary glands of the camel during the breeding season, and quotes Darwin[41] as to the thyroid and odoriferous glandular enlargement in various animals during this same season. Paget further suggests that the salivary glands may in some way have secondary sex characters, in the same category as the hair and voice. Cribb[42] cites 4 cases "which show the connection between the parotids and the prostate, vagina, and ovaries." Tayler[17] suggests a relation between the glands and the testes as an explanation of orchitis. He also cites numerous cases in which, following operations such as hysterectomy, ovariotomy, gastrostomy, circumcision, or in other cases such as lithotomy, typhus fever or penetrating abdominal wounds, a secondary parotitis developed, indicating a genito-parotid interrelationship. Wesselhoeft gives many citations from Owen,[43] Darwin and others to prove this relationship, among which are: (*a*) Musky odor from crocodiles' submaxillary gland at the breeding season; (*b*) enlargement of elephants' face glands at the rutting season (also applicable to the Indian antelope); (*c*) acute simple parotitis resulting from genital injury by such maneuvers as catheterization, prostatectomy, pessary insertion, pelvic operations, deliveries and abortions; (*d*) parotid swelling occurring with menstruation, replacing menstruation, with pregnancy, during and after the menopause; (*e*) postoperative parotitis as in Paget's cases.

A. Most authors regard orchitis as a true metastasis, or blood stream infection, localizing in the testis. Edwards[44] takes this view because of the rarity of primary orchitis. Walker[45] believes that, while the parotid is always involved in mumps, in certain cases the genital affection is so marked that the parotids remain unnoticed. Fougerousse[46] finds that the use of diathermy on the parotids is of value in the prevention of orchitis and thinks that this is good evidence for the metastatic mode of spread. Trousseau[19] says orchitis is a metastasis and that its occurrence proves the existence of a sympathy between the parotid gland and the genital organs. Wesselhoeft considers the extensive glandular involvement throughout the body an objection to any theory but the septic. He lists the glands and organs which may become involved: ovary, Bartholin's glands, mammary glands in males and females, lymph nodes, lachrymal sac, pancreas, thyroid, thymus, epididymus, prostate, bladder, urethra and genitalia. A case cited by Gould[47] and diagnosed "atypical mumps" was characterized by the involvement of one entire side of the body. Others[11, 48, 49] definitely state that the orchitis of mumps is not a blood stream metastasis.

B. Another theory that has been advanced is that infective matter is transferred from the mouth to the penis by the fingers, whence the urethra and subsequently the genitalia become involved.[12, 46, 50] This has been easily disproved by prophylactic experiments in which the hands were kept clean and the genitals surrounded by linen bags.[51] The incidence of orchitis was unaltered.

C. A third theory is that of glandular affinity and localization. This might operate by some means explainable by Rosenow's special affinity theory and that of Abderhalden as regards the chemotaxis of tissue cells to poisons and foreign substances. That the genital glands are merely one of the sites in the body affected by mumps is the theory held by Currier,[52] Comby,[6, 7] Gerard,[49] and Tayler.[17] I averan says that orchitis is merely a symptom of mumps in the same way as is parotitis.

D. Testicular trauma may predispose to orchitis[11, 12, 53] and it is also said that absolute rest in bed may help to prevent the onset of orchitic complications.[54] However, in two epidemics at Rugby in England, putting the cases to bed had no influence on the incidence of testicular involvement.[48] Moreover, cases of orchitis have been observed under circumstances where no possible trauma could have been sustained. Chill and exposure are probably not important factors in the onset of orchitis.[55] All these factors may, however, play contributory rôles.

Incidence of Orchitis. There is some confusion about this interesting and important subject, due to the fact that compilations of data by different authors not seldom overlap; and again, the figures quoted by different writers from apparently the same sources are at variance. Representative statistics are listed in the following

tabulation (Table 1). The average of the percentage incidence in those series comprising 1000 or more cases is 18.2%.

TABLE 1.—INCIDENCE OF ORCHITIS IN MUMPS.

Author.	Incidence in per cent of cases seen.	Cases.	Reference No.
Catrin	18.5	10,601	56
Wesselhoeft	18.0	8,000	12
Benard	15.0	5,000	57
Radin*	13.9	4,397	10
Benard	20.0	2,000	57
Longuet	25.0	1,555	58
Brooks	24.0	1,059	11
Comby	30.1	699	7
Capitan*	18.4	690	59
Granier*	23.2	495	27
Benard	22.0	408	57
Rilliet and Barthez	43.5	230	60
Philadelphia Hospital for Contagious Diseases	17.1	144	15
Thierry de Maugras	29.0	76	63
Chatin	24.3	37	64
Vidal	38.4	26	61
Busard	50.0	26	62
Hospital of Univ. of Pennsylvania	28.5	14	14
Laveran†	33.0	...	8
Hudelo†	60.0	...	65
Bieberbach and Vibber	18.0	...	66
Fougerousse	20.0	...	46
Macleod	20.0	...	67
Tillim	26.3	...	16
Tillim	75.0	...	16
Saucerotte	100.0	...	68
Chateauroux	100.0	...	69
Vedrennes	26.0	...	72

* Included in series of Wesselhoeft, reference 12.
† Quoted by Benard, reference 57.

It is interesting to note the age at which orchitis may develop. Acker[71] says that orchitis is rare in children. He quotes the observations of Rilliet and Barthez (taken from Holt[72]), which note that orchitis was seen in only 10 of 230 cases of mumps, 3 of these 10 under 15, and none under 12 years of age. Laveran[8] did not see orchitis in any boy under 14 in a large epidemic, and states that most of the cases were in the age group of 23 to 38. Lowe[73] observed most of his cases between 17 and 40. Stevens[74] regards this complication as uncommon before puberty. Béclère,[75] Dukes,[48] Sinclair[18] and a recent editorial writer[76] all say that mumps orchitis practically never occurs before puberty, and Vaughan[3] says that it never occurs before the 15th year. Wesselhoeft[12] observes that orchitis is usually confined to puberty and adolescence, but notes that there have been three exceptions: 1 in a 9 months' infant, 1 each in boys of 9 and 11 years of age. He also says that the incidence of orchitis decreases in direct proportion to the decrease of mumps in advancing years. Comby[7] cites cases of orchitis in boys aged 14, 12, 13, 9, 4

and between 15 and 17. In our series of the Philadelphia Municipal Hospital,[15] most of the cases were between 18 and 30, the oldest 52 and the youngest 17 (Fig. 1, A); all the cases at the Hospital of the University of Pennsylvania[14] were in the early twenties.

In a series of 694 cases, Macleod[67] observed that orchitis occurred in the second attacks of mumps in 17, and in the third in 1. Brooks[11] says that where there has been orchitis, the testes are sure to become involved again. Mitchell[77] has reported a case of mumps orchitis in an undescended testicle in a 33-year-old negro. Another such case in a boy of 14 was reported by Ross.[78]

The incidence of orchitis, then varies greatly with the author, the number of cases in each series, and the type of epidemic or environment. While the fluctuation is great, the majority of the larger series shows an incidence of about 18.2%; only 5 cases of orchitis have been reported prior to the 12th year; and occurrence of orchitis is generally limited to the time of puberty (the 14th to 15th year) or later.

Symptoms and Signs. The symptoms and signs which may be noted in a case of orchitis are varied and numerous, depending on a number of factors. The mode of onset, the severity of the affection, and the degree of involvement (unilateral or bilateral) are paramount.

TABLE 2.—DAY OF APPEARANCE OF MUMPS ORCHITIS.

Author.	Usually.	As early or as late as:	Reference No.
Macleod	7th	44th	67
Mitchell	7th	.....	77
Dukes	7th or 8th	.....	48
Catrin	4th to 8th	.....	56
Servier	3d to 6th	1st and 10th	24
Béclère	2d	.....	75
Wesselhoeft	Before subsidence of parotitis	.....	12

With regard to the mode of onset, most authors state that mumps orchitis is generally a sequel to mumps parotitis,[55] and this was the invariable finding in the two hospital series studied for this paper. The time of onset varies greatly (Table 2). It is stated[75, 56, 44] that exceptionally the orchitis may precede the parotitis (as far ahead as 13 days[79] or only 3 days[80]). Wesselhoeft[12] enumerates 30 cases and Comby cites cases of Saucerotte[68] in addition. The French literature contains numerous examples[66, 8, 74, 75, 81, 82, 45, 49, 83] of orchitis without any parotitis whatever. Some of these cases are listed by Wesselhoeft (64 cases) and Comby[6] has added others (84) among which are epidemics at Geneva and Danzig. Some of these cases have been termed "spontaneous" or "abortive" orchitis.[70, 56, 85, 87–90] Whether or not all of these are mumps is open to question.

The severity of the affection depends on the degree of involvement. When both testes are involved, the condition is certainly much more severe. Unilateral orchitis is commoner than bilateral, and it is said that the bilateral variety is very rare.[91, 74, 90] In a tabulation of 1200 cases[12] it would appear that the unilateral is two or three times as frequent. Other figures are given in Table 3. There

TABLE 3.—FREQUENCY OF BILATERAL ORCHITIS IN MUMPS.

Author.	Bilaterality, per cent of cases seen.	Reference No.
Madamet	0	92 (7 cases)
Macleod	16	67
Radin	20	10
Laveran	28	8
Smith, G. C.	30	93
Catrin	30	56
Wesselhoeft	25 to 35	12 (1200 cases)

is little difference between the frequency of involvement of the right and left sides.[8, 67] If the affection becomes bilateral, the second testicle is involved some time after the first, usually about the second day, and goes through the same cycle as did that first hit. Various attempts have been made to associate the side of the testicular involvement with that of the preceding parotitis, and to obtain some data from the severity of the parotitis in order to prognosticate as to possible orchitis and its severity. In general, there is no relation.[93] It has been stated[90] that orchitis is to be feared if there is considerable parotid swelling, submaxillary gland induration, and pronounced lassitude, but the sequence of events is not at all constant. Brown[55] reported 9 cases of orchitis where the involvement of the genitalia was ipsilateral with the parotitis in 8, and bilateral in the 9th. Acker[71] says orchitis is usually on the left side and on the same side as the "mumps." Many others disagree, saying what is generally accepted: that there is no relation whatever.

In general, the temperature is one's best guide, both in diagnosis of genital involvement at an early stage and in following its subsequent course. In the usual case, swelling and tenderness in the parotid gland on one or both sides has occurred and is practically subsided. The temperature starts to rise, and at the same time a certain malaise and anxiety is noted. Soon the patient begins to complain of tenderness in the body of the testicle on one side. Rapid swelling commences as the fever rises, and fluctuation may be noted.[67] (Edema usually appears on the 4th day, or often when the testicle is either enlarged or just starting to get smaller, but it is not always seen.) The slight tenderness increases in severity and soon gives way to very real pain, caused apparently by stretching of the tunica albuginea, the tunica vaginalis testis, and the scrotum. At the height of the involvement, usually on the 3d or 4th day, the

testicle may be enormously enlarged and the pain so severe that large doses of morphin will not relieve it. With the rise in temperature, which may reach 105° F., goes a parallel rise in pulse rate, while the respiratory rate may or may not be increased. Anorexia, thirst, weakness, headache, vomiting, "white tongue," and an "idle mind" are also observed.[90] The testicle becomes very hard and tense, and this condition may persist 4 to 6 days. Gradually the swelling subsides, and the fever drops. The recovery is slower than the involvement, and some fever may persist until all swelling is gone. Some authors describe a true crisis, at which time all the symptoms are exaggerated, and after which recovery is extremely rapid.[55] This probably occurs only in the most severe affections, and certainly the slow subsidence, or lysis, is more usually seen. The usual course of orchitis is about 10 days.[74] The testicle during the lysis becomes smaller, usually firm, but shows pitting pressure if there has been scrotal edema. Some authors say that the epididymus is the first genital structure to become involved, and that it is always implicated.[10, 54, 56, 90, 94] Others note epididymitis at a later stage only[19, 11, 24, 95] or not at all.[96] This is important from the prognostic point of view, since a temporary sterility may clear up if the trouble is only epididymal. The point is too controversial to be settled at the present time. It is generally said that primary epididymal involvement is seen in tuberculosis, gonorrhea, influenza and infectious diseases, but that genital affection in gout,[97] typhoid fever,[98, 97] undulant fever[70] and syphilis is orchitic. The spermatic cord and vas may or may not be involved.

Other rarer symptoms are noted from time to time. Oliguria, backache, nausea and vomiting may occur early in serious cases. On the other hand, polyuria, urethral discharges, chills and excessive perspiration have also been described, while some[44] say that urethral discharge, bladder irritation, suppuration and permanent changes in the epididymus are always absent. Rigidity and pain in the abdomen, especially in the inguinal areas along the course of the cord (*i. e.*, a deferentitis or funiculitis) have been cited by several writers as signs whereby appendicitis or other acute abdominal conditions have been confused with the true situation. In the very seriously affected, especially when the temperature stays as high as 104° to 105° F. for 24 to 36 hours, central nervous system symptoms such as delirium, stupor, and maniacal outbursts may supervene.[54, 94] In these cases, meningitis,[99] or encephalomyelitis[110] is sometimes suspected and may often be present (possibly the aseptic type), and the patient must be kept under severe restraint. There are many such cases recorded and the author knows of at least 3 other unreported occurrences.

A number of studies of the blood has been made on patients with orchitis. Investigators disagree on the findings. Feiling[54] states

that orchitis often does not affect the blood picture, and that while leukocytosis may be present in orchitis, there is also seen in many uncomplicated cases a rise in the white cell count of the order of 6000 to 13,500 with relative mononuclear increases. Wile[100] finds a constant lymphocytosis and a slight rise in the neutrophils at the onset of the orchitis. Bieberbach and Vibber[66] note a leukocytosis of 14,000 with 36% lymphocytes. In the 4 orchitis cases at the Hospital of the University of Pennsylvania, the white cell counts were 16,000, 9600, 18,600 and 12,800, while those in the uncomplicated cases varied from 4400 to 9800.

The failure to recover completely from orchitis is noticed subjectively in diminution in sexual power, or objectively in atrophy of one or both testes. It is generally said that "atrophy" of the testis occurs quite regularly.[13, 54, 7, 78, 74] This term is not at all clear, as it is frequently very loosely used. Most writers seem to mean only a reduction in size of the testis. With reduction of the enormous swelling and the cessation of pain the testes become soft and are then decreased in size by progressive stages. Later the testis may seem entirely normal or smaller than normal; and while the amount of reduction varies greatly[90] it may be only temporary, with a rapid return to its pre-orchitic size. Therefore, while an examination made immediately after recovery from orchitis may reveal a small testis, later examination would perhaps show one of normal size or of half the normal size.[57, 56] Statistics on "atrophy" following mumps orchitis are given by many authors,[6, 8] and its incidence is generally put at between 40 and 60% by most,[24, 27, 92, 101, 66, 56, 49] though higher (63%) by others.[8] However it may be that "atrophy" is only an anatomic occurrence (Bénard[57] states that he has seen but 2 cases of real atrophy, both unilateral), the fact remains that cases of physiologic atrophy are recognized. Bilateral "atrophy" is, of course, much rarer than the unilateral, and Granier[27] says few have been seen. Stevens[74] states that even bilateral atrophy does not mean loss of procreative powers. The cause of atrophy is essentially a pressure necrosis, and the results are aspermia and the loss of certain reflexes such as the cremasteric.[56] Wesselhoeft[12] describes areas of healthy tissue with normal functioning tubules separated by fibrosed areas of necrosis. There are usually no symptoms from an atrophied organ, but neuralgic pain may be manifest. The greater the severity of the orchitis, the better the chance of atrophy, and the more complete its degree. There are definite psychologic effects associated with testicular atrophy,[78, 102] but at the same time, it has been said[78] that an atrophied organ is better than none at all (*e. g.*, after removal by surgery). Orchitis does not always mean subsequent necrosis.

While the possibility of sterility following "atrophy" from mumps orchitis is mentioned by nearly all authors, yet only 2 cases of physio-

logically proven sterility are recorded.[102, 103] Wesselhoeft reports a sterile marriage after mumps orchitis; this, of course, proves nothing. He notes that cases of feminism have occurred, particularly that mentioned by Comby.[104] The latter says that effeminacy with enlarged breasts and eunuchoid voice can occur. Milder results than complete sterility, such as decreased sexual appetite or lessened ability to perform coitus (*i. e.*, impotence) are observed.[8] It is said,[12] however, that sterility results more often from atrophy of the prostate than that of the testis, and that the prostatic involvement should receive more attention. It is also a fact that bilateral orchidectomy causes prostatic atrophy. Therefore perhaps the prostatic involvement in mumps is secondary to the primary testicular lesion. Huber[105] remarks upon complete frigidity in a case, apparently a second orchitic attack. At the other extreme, Bénard[57] maintains that sterility from atrophy after mumps orchitis is practically unknown, stating that there was only 1 case in 175,000 cases of mumps in the French army, and he gives a number of statistics on these cases which might justify his stand. His chief arguments are: *a*, that the chances for bilateral orchitis after mumps are only 1½ to 2 in 100; *b*, that even partial bilateral atrophy is very rare; *c*, that after a suitable period of time many testes supposedly hopelessly atrophied were not so crippled and, *d*, that there are only 2 cases of functionally proved atrophy in all literature. Laveran[8] also belittles the possibility of sterility, quoting Velpeau[106] to the effect that "mumps is the least grave of all orchitis causes." On the other hand, many cases of sterility undoubtedly result, even though few[111, 112] appear in the literature. To support this statement, the author knows of 2 cases, communicated to him personally, which have resulted in total sterility, unquestionably due to the mumps orchitis which both patients contracted.

In addition to the case of feminism cited by Lereboullet,[102] another has been reported by Laignel-Lævastine and Courbon:[103] A young soldier, aged 22, tall, wiry, strong in every respect, and especially active sexually, contracted mumps which was complicated by double orchitis. He was hospitalized for 26 days, during which time his fever went over 40° C., he had neck pains and Kernig's sign, as well as a meningeal reaction (the spinal fluid showed increased albumin and 3 lymphocytes per cmm.). Seven months later his testicles were atrophying, his breasts were enlarging to the point of being clearly visible. Power of erection, sexual desire and vigor were all decreased, so that he felt a peculiar weakness after attempts at coitus. He grew weak after all forms of muscular exercise and his secondary sex characteristics changed to those of a woman. His legs were large, his abdomen big, his breasts quite enlarged, and his penis and testicles atrophied. There is apparently

no report on the subsequent progress of this case. It is most unusual, and it may well be that there was some endocrine factor in addition to the mumps.

Pathologic Anatomy. The pathologic changes occurring in the testicle during an attack of orchitis are almost entirely unknown, since surgical operations are but rarely performed, and as patients nearly always recover they do not come to autopsy.

A few cases have been operated upon. Smith[93] reported 2 in which operation was performed in the hope of preventing atrophy. In both of these there was considerable enlargement of the hard, smooth testicle. On incision of the tunica vaginalis, an ounce of yellowish turbid fluid, free of bacteria and parasites, was obtained. The testis appeared bluish, firm and elastic, and showed punctate hemorrhages. The epididymus was enlarged, soft, and red to black in color. The cord was edematous. In a microscopic study of 1 of these cases, a non-uniform involvement was specially noted. The tubules were distended with an exudate made up largely of neutrophils and endothelial phagocytes. Destroyed tubules, hyalin degeneration, and lack of mature spermatozoa were also observed. Between these destroyed tubules fairly normal tissue was seen, as well as a few sex cells in mitosis. The intertubular connective tissue was edematous and contained an exudate made up of fibrin, red and white blood cells. The impression was that the involvement had proceeded along the intertubular connective tissue or had progressed by way of the tunica albuginea. The latter was edematous and showed hemorrhages and exudation about the bloodvessels, but no necrosis.

Comby[6] cites the observations of Réclus[107] on a removed testicle. The gland was soft, flaccid and atrophied. The tunica albuginea was too large for its contained organ, and wrinkled. The substance of the testis was bloodless, opaline and milky white. The cut surface was smooth, showing tubules faintly marked, soft and easily broken. He regarded the underlying lesion as a parenchymatous sclerosis. Malassez[108] made histologic examinations of this organ, and reported the tubules diminished in volume, their epithelium gone, and their form similar to cords. He noted also healthy bloodvessels, and intercanalicular connective tissue that was not thickened. It is reported[12] that a serous exudate appears in the septa and lobules of orchitic testes and the tunica vaginalis is also involved. The scrotal skin becomes red and swollen, and the vas congested. In cats inoculated intratesticularly, epithelial degeneration and interference with spermatogenesis are found.[12] The inflammation seen in orchitis disposes to cancer according to some[78] and sarcoma has been recorded as a later development in such a testis. All other descriptions of the testicle in mumps orchitis are of its external appearance, essen-

tially the same as previously cited. There are some variations. Comby[6] notes that suppuration may occur late in orchitis, and that this may go on to a fatal peritonitis. He also recognizes a chronic orchitis. Ballenger and Elder[101] say that testicular destruction is probably due to some local toxic product of the organism causing mumps, or else it is a pressure necrosis only. If it is due to pressure, it is because the inflammatory swelling is prevented by the inelastic tunica albuginea.

Diagnosis. Little need be said on this topic, except that while orchitis is an easy diagnosis in the midst of an epidemic, it may become very difficult at other times. The history of contact must be carefully sought, and other causes of orchitis must be eliminated. It is said[6] that perhaps the involvement of the epididymus may distinguish the orchitis of mumps from that of gonorrhea.

There are a number of types of orchitis other than that occurring in mumps, in the same way as there are other forms of parotitis. Ballenger and Elder[101] list traumatism, gonorrheal infection, malaria, typhoid fever, scarlet fever, influenza, rheumatism, gout, and they also note that suppuration and atrophy are rare in these cases. To this list, Hughes[96] adds measles, also mentioning that mumps orchitis is by far the most frequent acute inflammatory swelling of the testicle. He notes that suppurative inflammation of the testicle can occur after infection of the bladder or urethra with Bacterium coli, especially in old men with prostatic obstruction. Bieberbach and Vibber[66] add paratyphoid fever, smallpox, tonsillitis and diphtheria to the long list. Various other types of orchitis are mentioned, mainly in connection with mumps, by French writers. Types such as the "abortive" variety, and the "spontaneous" forms, terms which are concerned with the time relation between parotitis and orchitis, come into this category.[6] A type of testicular involvement which Catrin[56] says must be distinguished from the orchitis of mumps because of its mild character is "fluxion testiculaire." A case has occurred in the Hospital of the University of Pennsylvania where a tuberculous origin was suspected.

Treatment. Treatment of orchitis is of two sorts: prophylactic and palliative. The first prophylactic measure to be thought of is the prevention of the disease. This may be accomplished by a quarantine of 21 days, as practised in certain localities for the prevention of contact spread.[13] Some regulations require isolation in separate cubicles. All these measures have been tried, in order to lessen the extremely rapid spread of mumps as observed in camps during the World War. The application of diathermy to the parotids has been mentioned under pathogenesis.[46] In the past several years convalescent mumps serum and, more lately, lyophile serum have been tried extensively[113-119] with very fair prophylactic success. In the prevention of complications in established mumps,

Sailer[51] and Wesselhoeft[12] say that all such measures as boiling utensils, cleaning the hands and preventing infection from reaching the urethra are useless. The faradic current has been used. Others[12, 67, 56] advise absolute rest for a long period after the onset of mumps as a measure to prevent complications, but it is also said[13, 66, 48] that the amount of bodily activity has no effect on orchitis. Some effects have apparently been noted from the use of convalescent serum as advocated by Gradwohl *et al.*[23] Ice packs, testicular elevation and dietary measures may be possible aids.[66]

Most authors say that one should make no attempt to manage the developed case of orchitis, since it must run its course in any event.[54, 8, 90]

There have been many measures suggested in the medical management, as is usually the case when no definite régime is recognized. The most important methods in use include rest in bed with elevation of the testicle and the use of the suspensory bandage. Heat, in the form of a hot-water bottle or poultice, especially combined with an emollient or belladonna ointment, or cold by means of an ice pack is very helpful. Manipulations should not be used in those cases where there is great pain. Other remedies more frequently used are listed for the sake of completeness: ammonium chlorid, tobacco poultices, phenacetin, salol, digitalis;[44] urotropin:[9] aconite, veratrum viride, pulsatilla, biniodid;[73] purges, bland diet;[67, 77] bromids, ichthyol, guaiacol;[13] and quinin mixture.[77] More lately convalescent serum has been tried and some success obtained. Its endorsers[23] say: "We were particularly struck by the remarkable effect of these injections upon the complication of mumps, to wit, a lessening of pain, and in earlier subsidence of swelling, together with an earlier drop in temperature." They saw relief of extreme pain from orchitis in 5 hours. In a recent case of bilateral orchitis,[120] marked improvement was obtained 36 hours after serotherapy. There is no good routine for the medical treatment of orchitis; it is merely symptomatic.

Some cases have been treated by surgery. Abraham[53] advised incision of the testis to relieve tension and prevent sterility. Ballenger and Elder[101] recommend anterior incision through the tunica albuginea in several places to allow bulging, followed by replacement of the organ and closure of the wound. Cases in this series that had been operated upon, and those done by Bieberbach and Vibber,[66] showed good results. Smith's 2 cases[93] were treated surgically for the same reasons and in much the same way. H. Smith[109] reports a case with marked relief after operation. Wesselhoeft says incision and relief of pressure may help very materially.

Recently advocated treatment by hypodermic use of antuitrin-S may alleviate sterility produced by mumps, though not enough cases have as yet been observed.[111, 112]

Summary and Conclusions. 1. Mumps is caused by a virus.

2. Orchitis in mumps is important because of the possibility of subsequent sterility or impotence.

3. There is a definite relation between the parotid gland and the genitals.

4. Orchitis usually follows parotitis and is more often unilateral than bilateral.

5. Orchitis is probably a hematogenous metastasis.

6. Orchitis is most frequent at the age of puberty; its incidence in a large number of cases is about 18.2%.

7. Rise in temperature; swelling, tenderness, pain in the testicle; subsidence of fever by lysis; later variability in size of the gland are prominent symptoms of orchitis.

8. Orchitis may be complicated by a number of conditions, among which may be included: *a*, Meningitis, and other central nervous system involvements; *b*, "atrophy" of the testis occurs in 40 to 60%; *c*, impotence and sterility certainly do occur.

9. The lesion in orchitis is probably a parenchymatous sclerosis.

10. Diagnosis in epidemics is easy; it may be difficult in the absence of an epidemic or of marked parotitis.

11. Prophylaxis is by prevention of the disease; treatment is purely symptomatic.

12. The use of convalescent serum or surgical incision may give good results.

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A ROUTINE DIAGNOSTIC PROCEDURE FOR THE PATIENT WHO ENTERS THE HOSPITAL IN COMA.

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Supplementing previous articles,[1,2] on the causes and differential diagnosis of coma in patients entering a general hospital, the present study aims to point out the need for a routine diagnostic procedure and to offer, from the experience gathered in this study, such a coma routine.

Of the 1167 patients (3% of the total hospital admissions) who entered this hospital in coma, in 1933, 1101 (94%) were diagnosed correctly on admission. It should be pointed out that 690 of these patients were in alcoholic coma, and 688 of these were correctly diagnosed on admission. Of the 477 non-alcoholic patients, 64 (13%) were incorrectly diagnosed on admission. Though these figures seem unusually good when compared to Bissell and Lecount's[3] statistics, the two studies are not comparable inasmuch as they analyzed only cases coming to autopsy, and the excluded recovered cases were probably easier to diagnose. In the total group of 66 cases which were incorrectly diagnosed on entry in our series, 47 resulted in death. We estimate that in 18 of these, death would possibly have been preventable if a correct diagnosis had been made on admission and appropriate treatment started at once. We further feel that the lack of a proper coma routine may have contributed seriously to the failure to make the correct diagnosis in these cases.

The medical student ordinarily receives very little instruction from the school and textbook in the practical matter of handling the patient in coma from unknown cause. The hospital intern soon acquires skill in this direction by experience. But the intern staff, which in the general hospital is the group responsible for the rapid and efficient analysis of these patients, is constantly changing. To insure uniform efficacy, it is suggested that a fairly rigid procedure be set up and followed by the house physicians as a coma routine.

From a consideration of the records of the 1167 patients previously referred to, the following data in relation to a coma routine have been accumulated.

The Importance of the History. Among the patients who entered the hospital in coma of non-alcoholic origin, the history was of immediate diagnostic importance in over 80% of the cases. Especially significant in the history were: the type of onset, injury, ingestion of poisons, infections, convulsions, headache and previous illness (diabetes, kidney trouble, heart trouble, high blood pressure). We estimate that among the cases incorrectly diagnosed, the lack of an adequate history was largely responsible in approximately 45% of the cases.

In view of the paramount, and, we may say, largely unappreciated, importance of the history in these cases, the authors feel that in coma cases every effort should be made to bring forth the history as soon as possible. The first representative of the hospital to see the patient, usually the ambulance man, should be instructed to bring to the hospital with the patient any relatives or friends who may help furnish the history of the case. If this is impossible, he should make every effort to obtain the essential points in the history while the patient is being made ready to leave for the hospital. A short delay at this time is far preferable in most cases to bringing the patient in without a history. If the ambulance man is unable to obtain a story, he should leave word with some responsible party that it may be "a life or death" matter to find out the patient's history and bring it to the hospital as soon as possible.

In spite of these precautions, patients will still be brought to the hospital without a history. The physician in charge should make it his first duty to have the police notified that the history in the particular case is a vital matter. The Boston police have been most coöperative in obtaining such histories for the hospital in a rapid and efficient manner. In some communities it may be that this function would be more suitably assigned to the social service department.

The Importance of the Physical Examination. It may seem unnecessary to stress the importance of a complete and thorough physical examination on every patient who is first seen in coma. But mistakes in diagnosis are not infrequently made because of an inadequate examination on patients considered alcoholic. The telltale odor of alcohol on the breath does not mean necessarily that the coma is due to alcoholism. In the group of incorrectly diagnosed cases referred to above, 5 patients were thought to be in coma because of alcoholism, whereas it developed later that 3 had severe brain injury with fractured skull, 1 had a subdural hematoma and 1 had lobar pneumonia.

The failure to examine the eyegrounds in 1 of the cases in this series resulted in an incorrect diagnosis in a patient with brain tumor. In 2 cases, the diagnosis of subarachnoid hemorrhage in 1 and meningitis in the other was missed because the examiner in each case failed to test for a stiff neck. Other points in the physical

examination which have been of particular diagnostic value in this series of coma cases are listed below in the summary.

From the practical standpoint, it cannot be overstressed that patients who enter the hospital in coma should be treated as emergency cases. The intern to be directly in charge of the patient should be called at once to examine the patient, preferably while the patient is still in the admitting room. Special diagnostic measures, if necessary, can then be undertaken without delay, and therapy started as soon as possible.

The Importance of Roentgen Rays. In some cases, Roentgen rays are of definite diagnostic value in determining the cause of coma. In the series of cases analyzed by the authors, they were of assistance in establishing the diagnosis in 74, or 6% of the total cases. Among the cases incorrectly diagnosed, they would have been of service in making the correct diagnosis in 15 cases, or 23% of the total cases incorrectly diagnosed.

The chief value of the Roentgen ray in these cases is as an aid in establishing the diagnosis of coma due to brain injury, through the demonstration of fractured skull. Roentgen rays of the chest are of diagnostic value in patients with coma due to pneumonia, or cardiac decompensation.

Because of the relative frequency with which fractures of the skull are overlooked in patients who enter the hospital in coma, Roentgen rays of the skull should be taken routinely on comatose patients who show evidence of injury. Unless the patient is in shock, they should be taken before the patient is sent to the wards from the admitting room, thus eliminating delay and unnecessary moving of the patient.

The Importance of Laboratory Work. It is well recognized that laboratory data can be of great assistance in making the diagnosis in cases of coma of unknown cause. In fact there is a tendency in coma cases to pay too much attention to laboratory studies and not enough to a careful history and examination of the patient. It is noteworthy, that in not a single case of those incorrectly diagnosed in this series, was the lack of sufficient laboratory data to blame. In our total series, laboratory work other than the lumbar puncture was of diagnostic value in 107 cases (9%).

The various laboratory procedures, and the relative order in which they should usually be done, are indicated below in the summary.

The Importance of the Lumbar Puncture. In some communities the lumbar puncture is still looked upon askance as a dangerous procedure, to be undertaken only on rare occasions by the neurologist or neurosurgeon. But the safety and value of the lumbar puncture in the hands of the general practitioner have been well established. In cases of coma of unknown origin we regard it, after the physical

examination and history, as the most important diagnostic procedure. In 174 cases, or 15% of the total cases in this series, the lumbar puncture was of critical diagnostic significance. Among the cases incorrectly diagnosed, 16 (24%) would probably have been diagnosed correctly had a lumbar puncture been done.

The lumbar puncture should be made a routine diagnostic procedure in cases of coma in which there is evidence of injury (except in the presence of shock), in cases with neurologic signs or symptoms, and in all cases where the diagnosis is obscure. The various observations and tests to be done on the cerebrospinal fluid are noted below.

Summary. The essential practical points in the above discussion have been abstracted and grouped in the form of a chart suitable for display in the hospital admitting room and intern laboratories (see chart). From the evidence presented, it is felt that the coma routine herein described will be of value in the proper handling of the patient who enters the hospital in coma.

Coma Routine. Patients entering the hospital in coma are *emergencies.* A life may depend on the rapidity with which a *diagnosis* is made and *treatment* instituted.

I. History. This is of paramount importance. If no friends accompany the patient, talk to the *ambulance man.* Then send out the *police* or a *social worker.* Inquire especially about: *type of onset, injury, alcohol, other poisons, infections, convulsions, headache, previous illness* (diabetes, kidney trouble, heart trouble, high blood pressure).

II. Physical Examination. Be rapid and thorough. Remember this is essentially veterinary medicine. Your patient cannot help you. Use your *eyes:* Note the patient's color, posture, movements; look for *wounds,* especially in the scalp. Examine the *pupils,* the *eyegrounds,* the *eardrums,* the *throat.* Use your *Nose:* Is there an odor to the *breath*—alcohol, acetone, illuminating gas? Use your *hands:* Feel for a *stiff neck,* for *fractures,* for *muscle* and *vasomotor tone* in the extremities, for enlarged *glands,* palpate the *abdomen,* test the *reflexes.* Use your *Ears:* Examine the *heart* and *lungs.* Take the *temperature, pulse, respiration* and *blood pressure.*

III. Roentgen Rays. Should be taken while the patient is on the way to the ward, unless the patient is in *shock,* when immediate shock treatment takes precedence over everything else. *Skull plates* should be taken in all injuries, and whenever the diagnosis is not evident. Other plates as indicated.

IV. Laboratory Work. (1) *Gastric lavage* for all poisonings, and severe alcoholics. *Save the contents.* (2) *Catheterize* and examine the *urine* as soon as possible. If reducing substances or acetone are present, and in all diabetics, do a *blood sugar* at once.* (3) Do

* Coma due to hyperinsulinism is recognizable by blood sugar estimation.—[Editors.]

the *routine blood* (red and white counts, hemoglobin and smear). In the presence of infection take a *blood culture*. (4) Take blood routinely on non-traumatic cases for a *Wassermann* and *non-protein nitrogen* determinations. (5) Spectroscopy, icteric index, van den Bergh, electrocardiograph, blood CO_2 combining power, etc., when indicated.

V. Lumbar Puncture. Routine in *all injuries* (except during shock), *cerebral vascular accidents, convulsions*, in the presence of signs of *increased intracranial pressure* or *meningeal irritation*, and in all cases *where the diagnosis is obscure*. Note the *initial pressure, color of fluid, red* and *white cell count* and *Ross-Jones* protein test. Remove enough fluid for *Wassermann, total protein* and *gold solution examinations*. When indicated, do *smear, culture* and *chlorid* and *sugar determinations*.

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PAGET'S DISEASE (OSTEITIS DEFORMANS).

Analysis of 116 Cases.

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The classic observations of Sir James Paget on osteitis deformans[1] have been confirmed and extended by subsequent investigations in various fields. Clinical reports on large groups of patients[2] have contributed in particular to the recognition and study of the disease in its early stages, an advance made possible by the introduction of roentgenologic examination. Biochemical research has provided a means of obtaining corroborating evidence in diagnosis through Kay's[3] discovery of the increased blood phosphatase activity in osteitis deformans. Extensive pathologic investigations, notably

those of Schmorl,[4] have facilitated the ultimate histologic diagnosis of the disease by establishing as characteristic a disordered "mosaic" architecture, resulting from the formation of irregular segments of lamellar bone, with prominent cement lines.[5]

Apart from their general interest, these advances have important implications in medical practice. It is now evident that the disease is not as rare as was formerly supposed but must be accounted among the more common primary affections of bone occurring after the third decade of life. The differentiation of Paget's disease from other diseases of bone, hyperparathyroidism for example, may be of vital importance in determining the course of treatment. The management of Paget's disease still presents many problems since treatment, except for palliative relief of pain in some cases, is unsatisfactory. The etiology of the disease remains unknown.

The observations recorded here are based chiefly upon the records of 104 cases of Paget's disease seen in the wards or outpatient department of this hospital from 1915 to 1935.* Of this number, 59 were seen from 1930 to 1934 inclusive, the total number of new patients treated during this period being approximately 200,000, of whom about 70% were over 30 years. Observations for a period of 5 years or longer were available in 26 cases. We had the opportunity to examine 77 cases of Paget's disease ourselves.

The diagnosis was established radiologically in every instance. With the exception of 3 very early cases, the lesions were sufficiently advanced to satisfy unequivocally currently accepted roentgenologic criteria of Paget's disease. In the early cases, the findings were limited to isolated areas of sclerotic condensation in a matrix of coarsely trabeculated bone. In addition to radiologic evidence, 41 cases presented deformities which made the clinical diagnosis obvious or probable. The phosphatase activity of the blood was determined in 76 patients[6] and found to be elevated in all but 1 early case.

Fifty-eight of the cases were males, 58 were females; 13 patients were negroes. No correlation between incidence and nationality or occupation could be established. No one station of life seemed to be particularly prone to the disease. In 4 instances, more than one member of the same family were found to be affected. In 1 case, 3 siblings and their mother presented the typical picture of the disease (Case 5, F. F.), in another 2 brothers and a son. The mother of a third case was shown to have osteitis deformans by radiologic examination elsewhere. Two of the cases in this series are brother and sister. Several other patients gave vague descriptions of other members of their families with moderate bowing of

* This study was made possible through the coöperation of the members of the medical, surgical and radiologic staffs. We are indebted particularly to Dr. W. W. Palmer and Dr. Ross Golden. We wish to express our appreciation also for the opportunity to examine 12 cases seen in other hospitals.

extremities or enlargement of the head, but these reports could not be investigated.

As in all previous studies,[2] the patients in this group were over 30 years of age when the disease was recognized (Table 1) with the

TABLE 1.—AGE INCIDENCE OF 116 CASES OF PAGET'S DISEASE.

Age in years.	25–29	30–39	40–49	50–59	60–69	70–79
Age when diagnosed, number of cases	1	6	22	34	40	13
Age at onset of symptoms, number of cases (27 cases asymptomatic)	2	9	29	35	12	2

exception of one patient who gave her age as 28. The figures relating to age when the first symptoms appeared are approximations only, as in some instances the onset was so insidious that the duration of symptoms could not be determined accurately; in others, it was not clear whether the symptom (pain, for example) should be attributed to Paget's disease or to coexisting pathology such as osteoarthritis or arteriosclerosis. No inference as to age at onset of the disease can be drawn from the age when symptoms first appeared, since the time which may elapse before bone lesions elicit symptoms varies widely in different patients. It is significant, however, that, so far as we have been able to determine, no authentic case of Paget's disease has been recognized in persons before the age of 25.

Twenty-seven cases had no symptoms or signs that could be referred to Paget's disease at the time the diagnosis was made. Skeletal changes were discovered fortuitously in the course of roentgenologic examination of the gastro-intestinal tract (12 cases), genitourinary tract (8 cases), paranasal sinuses (6 cases), or chest (1 case). In 12 of these patients subsequent radiologic examination of the skeleton showed fairly extensive Paget lesions which were entirely unsuspected by the patient or by the examining physician. There can be no doubt that a large proportion of cases of osteitis deformans escapes detection. Schmorl's systematic postmortem studies revealed an incidence of about 3% in persons over 40 years of age.[4]

In the 89 cases with symptoms referable to Paget's disease, within the limitations already alluded to, the course of the disease was usually so insidious that the patients did not apply for medical aid until many years after the onset of symptoms. Even then, in 25 cases, they consulted a physician primarily because of some unrelated disease. The initial manifestation of the disease appeared acutely in 18 patients, in the form of sharp pain (12 cases) or pathologic fractures (6 cases).

The initial and major symptoms of this group are summarized in Table 2. The most common first manifestation of the disease was

TABLE 2.—INITIAL SYMPTOM AND MAJOR SUBSEQUENT SYMPTOMS IN 116 CASES OF PAGET'S DISEASE.

	Initial symptom (number of cases).	Major subsequent symptoms (number of cases).
1. Pain back; hips; extremities	37	63
2. Headache	6	31
3. Deformities legs; spine; arms	17	48
4. Enlargement of skull	13	28
5. Fractures	6	16
6. Deafness	3	26
7. Difficulty in gait	5	38
8. Paresthesias	2	6
9. Vertigo	..	22
Asymptomatic	27	22

pain in the region of bone involvement, usually in the legs, lower back or hips. This was a dull ache, most frequently not sharply localized, usually worse after exercise and relieved by rest. Occasionally, the pain would occur at night. Varying degrees of stiffness in the joints were commonly associated with the pain. These complaints were generally considered "rheumatic" or "neuralgic" and often dismissed as due to "old age." The pain was rarely as severe or as generalized as in many advanced cases of hyperparathyroidism and more likely to mitigate or disappear spontaneously in the course of the disease. Definite bone tenderness was present in only 3 cases. Diffuse muscle pain and spasm were common accompaniments of deformities. Acute cramp-like muscle pain occurred most frequently in the calves of the legs. Thirty-one patients complained of pain in the head varying from an occasional headache, dull or throbbing in character, to the most excruciating recurring neuralgia. Many patients with obvious involvement of the skull had little or no headache.

No deformities whatever had been observed by the patient in 57 cases. Of these, in 45 instances no definite aberration from normal bone contours could be made out upon careful clinical examination of areas shown by Roentgen ray to be involved, sometimes quite extensively. This occurred most frequently when the pelvis and lower spine were the site of the lesion, less often when the bones of the extremities, more amenable to palpation, were involved. In only 17 patients had skeletal deformities advanced so far as to present the complete picture so graphically described by Paget (Fig. 1). The majority of cases (54) presented deformities but did not conform to the classic picture of the disease. Unilateral or bilateral bowing of the femora (usually with convexity of the lateral aspect), tibiæ (usually with convexity of the anterior aspect) or humeri were encountered, singly or in combination, with or without abnormalities of the spine and skull. Nineteen cases had markedly bowed extremities without obvious skull enlargement, 14 had massive heads without obviously deformed extremities. Eleven patients

had deformities of the radius or ulna, usually associated with changes elsewhere. In only 3 instances was involvement of the small bones of the hand or foot recognized.

Pain was usually present for some time before deformities were noted, but in 22 cases the appearance of deformities was preceded by no pain or by only slight pain. By the time any one bone was so extensively involved as to be obvious clinically, radiologic examination of the remainder of the skeleton almost invariably revealed lesions elsewhere. This obtained also for the tibiæ which appeared to be normal clinically in 16 cases presenting advanced deformities in other bones. While abnormalities of the tibiæ may be the first or

FIG. 1.—M. P. Advanced Paget's disease, showing marked asymmetric enlargement of the skull (64.2 cm.), with parietal bossing. An unusual feature is the involvement of the mandible, which is apparent.

only sign of the disease, and are easy to palpate, the importance of bowing of the tibiæ as an early clinical sign of Paget's disease has been overemphasized, we believe. Deformities in persons under 40 years of age are rarely due to osteitis deformans. But Paget's disease must be considered among the more common non-traumatic causes of deformities in extremities developing late in life.

Marked bowing of a long bone may lead to the development of numerous incomplete fissure fractures of its convex aspect (Fig. 2*a*). Pathologic fractures, characteristically transverse, usually follow (Fig. 2*b*). In 14 cases, fracture after little or no trauma had occurred, in 6 instances without preceding pain in the affected limb. Compression fractures of the spine, apparently asymptomatic, were discovered in the Roentgen ray films in 3 instances. Most frac-

tures healed firmly with abundant callus (Fig. 2*c*) usually within the period required for union of normal bone.

Fatigability and moderate general muscle weakness were common, particularly in patients with deformities of the lower extremities. As bowing with shortening of one leg progressed, limp developed (Fig. 3) and as deformities advanced, locomotion became more and more labored; 12 patients could not walk unsupported, some

FIG. 3.—L. M. Moderately advanced Paget's disease. To show characteristic posture noted in many cases where there is marked shortening of one leg.

could not even stand. Marked muscle atrophy and some decalcification of the bones due to disuse were common in such cases. For the most part, however, as Sir James Paget pointed out,[1] patients with osteitis deformans are able to support their weight in spite of extreme deformities of the lower extremities. In 7 cases, difficulties in gait became manifest in the absence of any bowing of the legs or were wholly disproportionate to the mechanical disability present. Such patients developed an uncertain, broad-based waddle and

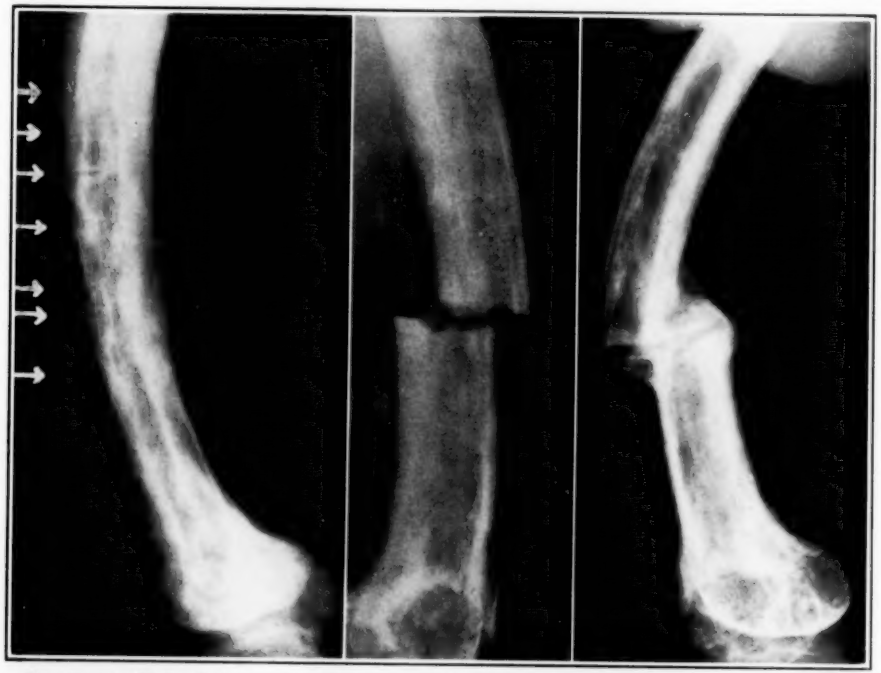

FIG. 2.—*A*, H. S. Left femur with numerous incomplete fissure fractures through the convex aspect. *B*, R. N. Left femur with a typical transverse fracture. *C*, R. N. Abundance of callus formation usually seen in healed fractures through Paget bone.

FIG. 4.—M. S. *A*, Lateral view of the right tibia in 1927. *B*, same in 1935. Note extension of the process distally, with increased expansion of the cortex and more marked bowing.

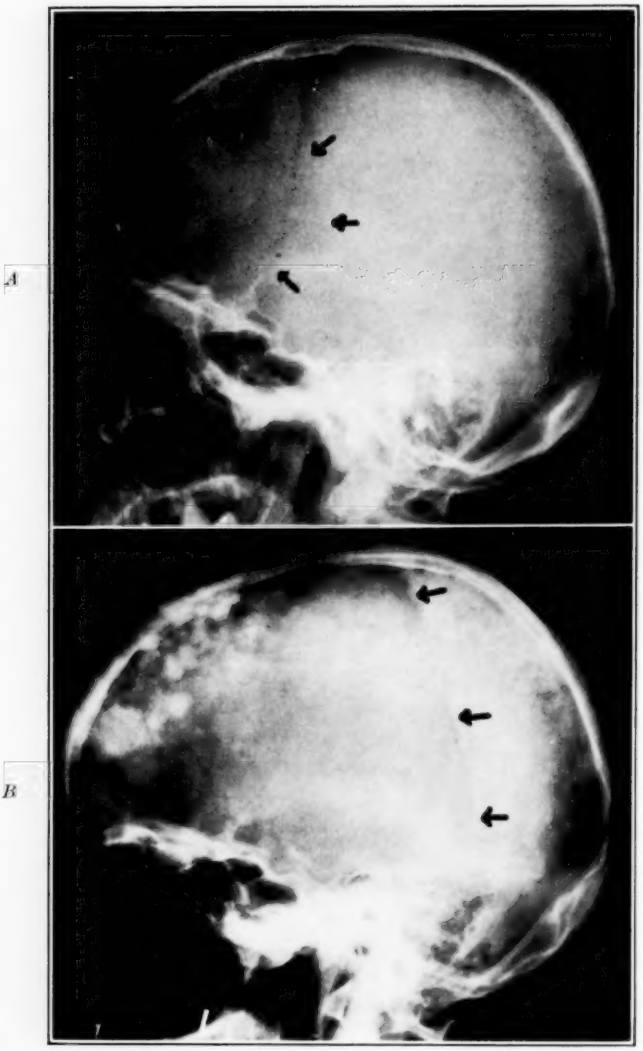

FIG. 5.—M. S. *A*, Lateral view of the skull in 1925. To show osteoporosis circumscripta associated with typical Paget lesions in other bones. *B*, same in 1935. Typical "cotton-wool" areas have now appeared. The osteoporosis circumscripta has extended posteriorly almost to the occiput.

characteristically progressed by supporting themselves on successive fixed objects in their paths. Incapacitation was likely to progress more rapidly and to become more complete when due to impingement of bone upon the cerebellum, spinal cord or spinal nerve roots than when due to bowing or other mechanical difficulties.

The infrequency of predominating psychic or neurologic symptoms has been commented upon many times, since contraction of the vertical diameter of the cranium[7] and of the lumen of the spinal canal and nerve outlets[8] may be striking. Two cases in this series had dementia, 2 others were paranoiac. As the skull was markedly involved in all these cases, there may have been some relation to Paget's disease. Symptoms suggestive of cerebellar ataxia, seen in some of our cases, may be inconspicuous despite roentgenologic evidence of marked cerebellar compression. Impairment of hearing was the most common manifestation of cerebral nerve involvement. Twenty-six patients complained of deafness but in many instances this was the result of infection or, where audiograms were obtained, was shown to be due primarily to faulty bone conduction. Impairment of vision was not uncommon but was the result of optic atrophy in only 4 instances. For the most part, changes in the eyegrounds were secondary to sclerosis of the retinal vessels which was present in some degree in most patients. Case J. R. illustrates the occasional association of angioid streaking with Paget's disease. Numbness and tingling of the feet was the initial symptom in 2 cases. How much of the disability and pain observed in many cases should be attributed to nerve impingement is uncertain.

Our series is unusual in that sarcomatous degeneration was not observed. One case died of sarcoma but this was thought to be unrelated since postmortem examination showed the tumor to be of the reticulum cell type. Another case, suspected of early sarcomatous changes, is being followed.

Roentgenologic Considerations. The importance of roentgenographic examination is illustrated by the fact that clinical evidence sufficient to warrant the diagnosis of osteitis deformans was absent in almost two-thirds of our cases. In all cases, radiologic study was considered essential for confirmation of the diagnosis as well as for determining the extent and character of the pathology in various bones. Recapitulation of the characteristic and well-known roentgenographic features of Paget's disease is unnecessary here.[9] Only specific details will be considered, particularly those relating to bone changes disclosed by follow-up studies, in some instances of 10 years' duration.

In 14 cases the lesions appeared to be localized to a single area. Of these, however, 8 were in the skull or pelvis and involved at least two adjacent bones, so that the term "monostotic" could be applied properly to only 6 cases. Early lesions in a long bone were

confined almost invariably to one end of the shaft, the remainder of the bone being apparently normal (Fig. 4); or both ends of the shaft were involved and in the course of time appeared to converge toward the midshaft. In the pelvis, early lesions were seen most frequently in the area comprising the bodies of the ischium, pubis and ilium, medial to the acetabulum. In many of the early cases, only one side of the pelvis was involved. The marked deformities seen in some pelves due to upward and inward protrusion of the heads of the femora, as well as the bowing of weight-bearing long bones, reveal the softening of bone which may take place in this disease. In many instances, different bones or even different areas of the same bone presented strikingly varied lesions ranging from local or regional osteoporosis with coarsened trabeculations to dense osteosclerosis. In several cases, the development of sclerosis in striated areas could be demonstrated in subsequent films. Osteitis deformans may become arrested at any stage as shown in Case M. S., where the lesion in the pelvis remained practically stationary in the coarsely striated stage for 10 years. It would seem hazardous, therefore, to draw from a single roentgenogram, any conclusions as to the activity of bone changes or to predict the course of the disease.

TABLE 3.—INCIDENCE OF INVOLVEMENT OF DIFFERENT BONES IN 116 CASES OF PAGET'S DISEASE.

Skeletal distribution.	Number studied.	No. not involved.	No. showing involv.	Early changes	Advanced changes	Bilateral involv.
Skull*	105	23	82	17	65	
Scapula	63	45	18	4	14	8
Clavicles	63	48	15	6	9	10
Ribs	63	55	8	4	4	3
Cervical spine	46	41	5	..	5	
Dorsal spine	64	38	26	8	18	
Lumbosacral spine	92	41	51	17	34	
Pelvis	101	11	90	10	80	
Humerus	63	26	37	10	27	11
Radius	27	20	7	6	1	
Ulna	27	22	5	4	1	
Hands	8	7	1	1		
Femur	91	32	59	8	51	33
Patella	60	59	1	1		
Tibia	63	29	34	7	27	14
Fibula	63	59	4	4	..	1
Feet	6	5	1	1		

* In 3 cases, osteoporosis circumscripta of the skull was the only skull manifestation, with typical Paget changes elsewhere.

In the skull, early "cotton-wool" changes were seen most frequently in the frontoparietal or frontal region, rarely in the occipital region alone. Involvement of the base of the skull (7 cases) or of the facial bones (6 cases) was unusual and was never seen unless advanced lesions of the cranial vault were present. Osteoporosis circumscripta of the skull[10] was observed in 10 cases, together with a "cotton-wool" appearance of the calvarium (7

cases) or as the only skull change associated with Paget's disease elsewhere. Follow-up studies showed that typical lesions of osteitis deformans developed in the osteoporotic area which itself expanded during this period (Fig. 5; see Ref. 10 for other examples). Osteoporosis circumscripta should not be confused with the multiple rounded areas of local osteoporosis often surrounding "cotton-wool" lesions in the calvarium.

Generalized decalcification of the skeleton, of the type seen in hyperparathyroidism, was not encountered. Varying degrees of osteoporosis were seen associated with coexisting marked arthritis or where the patient was confined to bed as the result of fractures or deformities. Cystlike changes, thought to be fatty-marrow spaces,[5] were seen occasionally at the proximal ends of the femora or humeri. Fractures, described above, occurred most frequently in the femora, humeri and tibiæ.

The incidence of osteitis deformans in various bones in these cases is summarized in Table 3. The pelvis, skull, femur, humerus, lumbosacral spine and tibia were most commonly involved.

Biochemical Considerations. The blood constituents of chief interest are those most intimately concerned with bone metabolism, so far as they are known: calcium, inorganic phosphorus and phosphatase. As reported in most recent studies,[11] the serum calcium and inorganic phosphorus are within normal limits, whereas the blood phosphatase activity is increased. Of the 78 cases examined, the serum calcium was between 9 and 11 mg. % in 69, between 11.1 and 11.5 mg.% in 8. In 1 patient repeated values over 12 mg.% were obtained, apparently due to complicating factors and not to the localized Paget lesion present.[12] Recent investigation warrants the conclusion that the diagnosis of uncomplicated Paget's disease is doubtful where repeated analyses by competent observers show elevated serum calcium values.

The serum inorganic phosphorus in the 77 cases examined was not less than 2.7 mg.% or more than 4.2 mg.% except where associated renal impairment caused retention. With the exception of 1 early case, the determination of serum phosphatase activity in 76 patients uniformly yielded values exceeding 4 Bodansky units (the maximum for normal adults[11d] by Bodansky's method). Our results favor the view that the level of blood phosphatase activity in this disease is determined largely by the extensiveness of skeletal involvement, as shown by Roentgen ray (Fig. 6). In our 5 most advanced cases, the values ranged from 130.3 to 59.5 Bodansky units. In our 10 cases presenting only early localized lesions, the blood levels ranged from 8.3 to 4.5 Bodansky units, with the exception of 1 case in which a value of 1.8 Bodansky units was obtained. In 13 of 15 cases presenting advanced involvement of one area with early lesions elsewhere, the spread was between

20.8 and 4.1 Bodansky units. In the 2 remaining cases, in which the skull was maximally involved, the values were 53.6 and 49.1 Bodansky units. In the remaining group of cases, the most common type encountered, presenting advanced polyostotic lesions, there was a diffuse scatter over a very wide range: 120.6 to 9.7 Bodansky units. In this group particularly, disproportionately high values may be found in cases presenting an unusually rapid course and unexpectedly low values may be encountered in cases clinically quiescent. It would appear, therefore, that the rate at which the

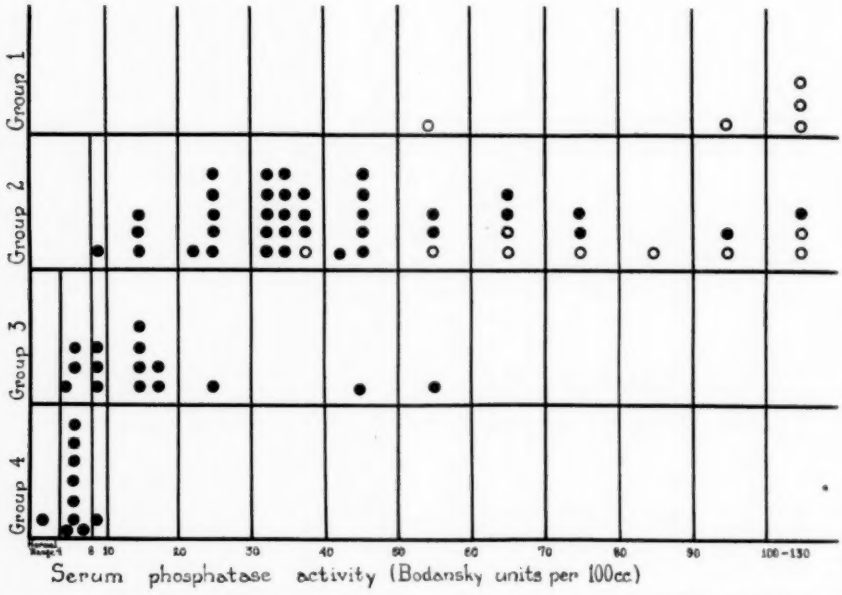

FIG. 6.—Distribution figure to show the correlation between serum phosphatase levels and extensiveness of bone involvement in 76 cases of Paget's disease. The cases are divided arbitrarily into four groups, according to the extent of bone involvement as shown by Roentgen-ray. Group 1 comprises the most advanced cases, Group 4 those with early localized lesions (see text). The hollow dots represent cases progressing relatively rapidly.

disease progresses may affect the level of blood phosphatase activity in osteitis deformans[2c,2d,11d] and that the determination is of some value in prognosis.

A significant finding not emphasized in the literature is the constancy of the serum phosphatase level in many cases of Pagets' disease when determined at intervals (see case histories). In exceptional instances, however, wider variations were encountered as in Case J. W., whose blood showed 94.3 Bodansky units in 1934 and 60.6 Bodansky units in 1935. As is well known, markedly increased blood phosphatase activity is not specific for Paget's

disease but may be encountered in several conditions where there is an increase in processes leading to bone formation,[13] or with liver damage.[14] Its determination may give valuable corroboratory evidence in diagnosis and also information as to activity, but it is of no value in differentiating from osteoplastic carcinoma metastases, particularly in carcinoma of the prostate.[12] While sometimes helpful in early diagnosis, often, in our experience, the bone lesions must be sufficiently far advanced as to be obvious radiologically before the increase in serum phosphatase activity is unequivocal.

Five case reports, each representative of a group of patients, have been selected for summarization. The cases illustrate how widely the course of the disease may vary, depending in large part upon the purely mechanical effect of Paget lesions as determined by their location, extent, stage and rate of development. Cases 1 (M. S.) and 2 (L. M.) represent the most common types encountered, in which deformity or pain was the chief complaint. Both patients presented very similar findings at the time of their first examination 10 years ago. M. S. has remained free of serious symptoms whereas L. M. has become completely disabled. M. S. is interesting also because of the associated osteoporosis circumscripta of the skull. Case 3 (J. R.) illustrates the course of the disease when neurologic symptoms due to compression of the spinal cord, brain or nerve roots predominate. In Case 4 (A. O.), the clinical course was determined by the occurrence of fractures and their complications. This was one of the few instances where the differentiation from hyperparathyroidism offered any problem. Case 5 (F. F.) is typical of a number of patients in whom deafness is the most distressing symptom. The case is of special interest because of the unusual familial incidence of Paget's disease.

Case Abstracts. Case 1.—M. S., an American housewife, aged 43, was admitted to this hospital in 1925 because of acute appendicitis. Appendectomy was performed, with uneventful recovery. An incidental finding was an irregular swelling and anterior bowing of the left tibia suggestive of Paget's disease. No other deformities were demonstrable clinically. The bowing of the left leg, first noted by her in 1918, had slowly progressed. She had never had pain in that leg or elsewhere, nor were other symptoms or signs of osteitis deformans present. She was the only member of the family affected.

The Wassermann reaction of the blood and urine analyses were negative. Radiologic examination disclosed characteristic coarse trabeculations and expansion of the left tibia, pelvis, sacrum, distal third of the right femur, upper third of the right tibia, head of the right humerus, and second metacarpal of the left hand. The skull showed only an area of osteoporosis circumscripta in the right frontoparietal region (Fig. 5*a*). The lumbar and dorsal spine, thorax, shoulder girdle, left femur and fibulæ were normal. Reëxamination of the skeleton in 1927 disclosed no apparent change except the development of a few sclerotic islands in the area of osteoporosis circumscripta. Reëxamination in 1935 revealed extension of the area of osteoporosis circumscripta and an increase in "cotton-wool" islands within it (Fig. 5*b*). The tibiæ were more bowed, especially on the right side which

now showed involvement of the upper two-thirds and increased cortical thickening and expansion. In the right femur the changes now extended to the neck. There was a slight increase in the process in the pelvis without sclerosis. There was no definite alteration in the appearance of the spine. Examination of the blood (1934) showed serum calcium 10.2, serum inorganic phosphorus 3.8, serum non-protein nitrogen 32 mg. per 100 cc., and serum phosphatase 34.6 Bodansky units per 100 cc.

Her course has been practically asymptomatic. Her legs began to tire easily in 1927 and this has led to some restriction of activity in recent years. Since 1930, the right tibia has become progressively bowed anteriorly. In 1934, she experienced occasional cramps in the calf muscles. Apart from this she has been entirely free of pain, her gait is affected but little, her head has not increased in size, she has had no headache, hearing and vision are unimpaired. She is (1935) an alert woman who performs her daily household activities without difficulty. She presents no clinical stigmata of Paget's disease except bowed tibiæ.

Case 2.—L. M., a Jewish male, mechanic. There is no familial or childhood history of bone disease. In 1925, when 43, a friend pointed out a slight bowing of the right leg. The leg began to ache several months later. He went to the Neurological Institute, where radiologic examination (Dr. C. W. Schwartz) revealed advanced Paget's disease of the right femur and of the skull, with earlier lesions in both humeri, scapulæ, the left clavicle and left femur. Reëxamination in 1927 showed additional changes in the pelvis. The Wassermann reaction of the blood was negative. Examination of red cells, hemoglobin, leukocytes, calcium, urea, uric acid and sugar in the blood gave normal values. The urine was negative.

Because of continued severe pain in the right leg and lower back, he applied to our outpatient department in 1930. Limp had developed as a result of increased bowing and shortening of the right leg. He was treated with a variety of glandular preparations, baking and massage, and various analgesics without relief. His course since then has been one of progressive and relatively rapid incapacitation. Pain and increasing difficulty in gait have made work impossible since 1932. A rounded dorsal kyphosis, enlargement of the skull and bowing of the left femur, all first noted in 1932, have increased markedly. His stature has decreased from 5 feet 7 inches to 4 feet 6 inches. The deformities of the femora have made walking so painful, labored and fatiguing that, even with the help of a cane, he can negotiate only short distances. Hearing is impaired on the right side, audiometer readings indicating moderate nerve deafness. The tibiæ show no changes clinically. He has had no headache. Radiologic examinations have shown increasing involvement of the skull, with encroachment upon the bones at the base, and advanced lesions particularly of the pelvis, spine and both femora. There is marked arteriosclerosis. His eye grounds also revealed sclerotic vessels and in addition suggestive angioid streaking.

A course of radiotherapy to the involved bones has relieved his pain considerably. There has been no significant change in blood values as a result of treatment. In September, 1934, chemical examination showed serum calcium 10.7, serum inorganic phosphorus 3.2, serum non-protein nitrogen 32 mg. %; serum phosphatase 122.2 Bodansky units per 100 cc. In March, 1935, the values were 10.2, 3.4, 23 and 116 respectively.

Case 3.—J. R., a Jewish housewife, aged 54, was admitted to this hospital in October, 1934. Her familial history was irrelevant, except for a paternal uncle who was said to have had deformities suggestive of Paget's disease. She had been well until 1924 when she complained of occasional attacks of "neuritis" in the shoulders and legs, accentuated by exercise, and relieved by rest. In 1927 she began to have intermittent occipital headaches of "burning" character. These have increased progressively

in severity and duration and for the past 5 years have been almost unremitting. She noticed enlargement of the skull about this time. Radiographs of the skull in 1928 disclosed Paget's disease. In 1929 she noted bowing of the legs and complained of pain in the knees and in the calf muscles of both legs. In 1930 increasing kyphosis of the upper dorsal spine developed, with tenderness of the spine between the shoulder blades. About this time her gait became unsteady. She fell several times, on one occasion fracturing her right arm. The uncertainty in gait was not due to weakness but to loss of sense of balance. For a time she was able to walk by steadying herself on fixed objects, but has spent most of her time in bed in recent years. By 1930 her head was so large that she had difficulty getting hats to fit her. In 1931 she began to complain of dysphagia and regurgitation and has had to limit her diet to soft foods since then. She attributes a loss of 30 pounds in the 2 years following to difficulty in swallowing. This has improved in the last 2 years and she has recovered most of the weight lost. In 1931 photophobia developed, without impairment of vision. She has had to wear dark glasses for several years. Deafness of the left ear, with occasional tinnitus, has been noted since 1932. In 1932 she complained of paresthesias of the fingers of both hands and found that she was unable to tell whether she had succeeded in grasping small objects unless she looked at her hands. In 1933 her speech became thick. She has been orthopneic for 2 years. Her presenting symptom when first seen was headache.

On admission she was markedly deformed and wholly incapacitated but withal cheerful and mentally alert. The skull was markedly and asymmetrically enlarged with a prominent bulge in the left parietal region. The neck was short and almost immovable, the chin resting on the sternum. There was a kyphoscoliosis of the spine with an angular deformity in the upper dorsal region. The thoracic cage was fixed, the clavicles thickened and protruding. Both femora, humeri, radii and the left ulna were thickened and deformed. The tibiæ appeared to be normal. Examination of the eyes showed irregular horizontal and vertical nystagmus with weakness of the right inferior rectus muscle. There was no papilledema, temporal pallor of the disks was within normal limits. Retinal vessels were sclerotic. Typical angioid streaking of the retina was present. Examination of the chest, heart and abdomen disclosed arteriosclerotic heart disease with moderate passive congestion of the liver.

Neurologic examination showed a positive Romberg test, the patient being unable to stand without support. Deep reflexes could not be elicited even with reinforcement. Suggestive Babinski and Chaddock responses were obtained on both sides. There was considerable uncertainty in the heel-to-knee test. There was a loss of vibratory sense over both lower extremities and pelvis, preserved over the upper extremities and spine. Abdomen reflexes were absent. The muscles of both legs were markedly atrophied. There was no apparent weakness or atrophy of the tongue, palate or pharyngeal muscle groups. Attempts to drink fluids, however, revealed difficulty in swallowing. The findings suggested encroachment upon the brain and spinal cord.

Radiologic examination showed marked involvement of the skull including the bones at the base. The floor of the skull was convex ("convexobasie"). The vertical diameter of the skull and the dimensions of the cerebellar fossa were markedly diminished. The pelvis, spine, femora and right humerus were involved. The tibiæ were normal. Marked arteriosclerosis was present.

The visual fields were contracted, suggesting impingement of bone upon the optic foramina but stereoscopic films of the optic canals revealed these to be normal in size and contour. Fluoroscopic examination of the esoph-

agus showed no abnormality of lumen or contraction. The dysphagia appeared to be due to difficulty in initiating upward and forward movements of the tongue and larynx as the barium bolus slipped backward from the base of the tongue. It was felt that this might be due to a central lesion.

The Wassermann reaction of the blood was negative. The red cells, leukocytes and hemoglobin of the blood were normal. Examination of the urine was negative. The serum calcium was 10.6, serum inorganic phosphorus 3.7, non-protein nitrogen 28 mg. %; the serum phosphatase was 117.5 Bodansky units per 100 cc.

CASE 4.—A. O., an American woman, aged 60, was admitted to this hospital in October, 1933, because of inability to stand since sustaining a fracture of the right femur 2 years before. There was no familial history of bone disease. Her history was irrelevant until 1928 when she complained of "rheumatic" pains in the lower back, hips and right leg, associated with stiffness and unusual fatigue. In 1929, she noted increasing deafness on the right side with occasional tinnitus. In 1931, she fractured her right femur after a slight fall, with firm union in 6 weeks. Radiologic examination revealed extensive skeletal changes interpreted as Paget's disease, though with marked associated decalcification. Three months after the first fracture, while on crutches, she fell and sustained another fracture of the right femur. The fracture healed well in 2 months. Nevertheless, she was confined to bed or to a wheel chair for the next 2 years because the right leg had become too weak to support her. There was some increase in the size of the head in the past year. There was practically no pain, no headache, no vertigo. No obvious deformities had developed. Vision was unimpaired.

Examination showed a well-preserved, rather obese woman. The positive findings were a moderate enlargement of the head, some impairment of hearing, marked atrophy of the muscles of the right leg and generalized arteriosclerosis with moderate elevation of blood pressure. There was some thickening of the distal end of the right femur but no other deformities were present. Neurologic examination failed to show any abnormalities. Radiologic examination revealed advanced Paget's disease of the skull, pelvis, spine, right femur, right tibia and right humerus. The pelvis, spine and bones of the right leg showed, in addition, a degree of osteoporosis unusual in uncomplicated Paget's disease. It was felt that this was due to disuse. Marked arteriosclerosis was present.

The Wassermann reaction in the blood was negative. The red cell, hemoglobin and leukocyte content of the blood were normal. Urine analysis was negative. On October 3, 1933, the serum calcium was 10.1 mg. %, serum inorganic phosphorus 2.9 mg. %, serum phosphatase 88.7 Bodansky units per 100 cc. Three days later, the values were 10.3, 3.1 and 88.1 respectively. Calcium and phosphorus balance studies were carried out. She was placed on a neutral ash diet approximating 100 mg. calcium and 400 mg. phosphorus a day (determined by analysis of aliquots) for 6 days. The output in stool and urine was then estimated for 2 three-day periods. Her average daily output of calcium on this regimen was 0.252 gm., of which 32% appeared in the urine. The average daily negative calcium balance was 0.147 gm., the average daily negative phosphorus balance was 0.175 gm. These values fall within the range observed in normal persons on similar diets.

It was felt that the possibility of hyperparathyroidism, which had been considered, was excluded. In the belief that the weakness of the right leg, her presenting problem, was due to secondary muscle atrophy and osteoporosis, she was given a high calcium diet with viosterol and the right leg was massaged and exercised regularly. In a few months she was able to

get about in a "walker" at first supporting her weight largely with her arms. By May, 1934, she could support her weight on her right leg without difficulty. Muscle atrophy was less marked. Roentgen rays showed slight increase in density of the decalcified bones. The serum calcium was 10.1 mg. %; serum inorganic phosphorus, 3.5 mg. %; serum phosphatase 91.9 Bodansky units per 100 cc. At the suggestion of Dr. C. R. Murray broad based tripod crutches were gradually substituted for the "walker." In the course of the next year she could get about surprisingly well. In 1935, the serum calcium was 10.2 mg. %, serum inorganic phosphorus 2.5 mg. %, serum phosphatase 90.4 Bodansky units per 100 cc.

Case 5.—F. F., an American salesman, aged 69, came to this hospital in June, 1934, because of deafness. His family history was extraordinary. His mother was described as having had a very large head, together with bowing of the legs which had developed after the age of 45. A sister had advanced Paget's disease, verified by radiologic examination. A brother, now 80, presents a classic picture of Paget's disease with marked bowing of the legs, difficulty in gait, moderate enlargement of the skull and deafness.

The patient noted an increase in the size of his head 20 years ago. For many years his hats have been specially made for him. In 1925, bowing of the right femur developed, subsequently causing shortening of the right leg and limp. This has not proven a serious handicap, however, as it has been his custom for years to walk several miles a day without the use of a cane and without fatigue. Since 1917 deafness has been his chief problem. There is a total loss of hearing on the right side and marked impairment on the left, which forced him to give up his work. His skull had been Roentgen rayed several years before; advanced Paget's disease was found. He denied ever having had pain, vertigo or headache.

Examination disclosed a remarkably well preserved man. His skull was markedly enlarged with prominent bulging of the parietal bones on both sides, separated by deep fissures from the domelike vertex; The skull measured 26½ inches in its greatest circumference. The right femur was bowed. No other abnormalities, except the deafness, were noted. The tibiæ appeared to be normal. Examination of the blood showed (mgm. per 100 cc.) serum calcium 10.7, serum inorganic phosphorus 3, serum non-protein nitrogen 36; serum phosphatase 72.6 Bodansky units per 100 cc. In March 1935 the values were 11, 3.2, 37 and 77.6 respectively.

Differential Diagnosis.—Even early localized Paget's disease, without clinical manifestations, presents so distinctive a roentgenologic picture that there is usually no question as to diagnosis. Our most common problem was to distinguish osteoplastic skeletal metastases secondary to prostatic carcinoma from sclerotic Paget lesions. While the clinical findings and course usually revealed the primary tumor, in occasional cases rectal and cystoscopic examination were equivocal and urologic symptoms, loss of weight and anemia were absent or mild. The radiologic manifestations in both diseases may be very similar but, as Sutherland[15] pointed out, metastases cause no expansion of bone contours, coarse striations are never seen, the skull changes when present do not show a typical "cotton-wool" appearance and osteolytic lesions are usually discernible somewhere in the skeleton. The serum phosphatase activity may be as high in cases with extensive osteoplastic skeletal metastases as in advanced Paget's disease, the serum calcium and

phosphorus remaining within normal limits.[12] Osteoplastic metastases arising from sites other than prostate gland did not present any difficulty in diagnosis.

There was rarely any question as to differentiation of osteitis deformans from generalized osteitis fibrosa cystica (hyperparathyroidism). The clinical findings and course are usually sufficiently diverse to distinguish the advanced forms of these diseases. In classic hyperparathyroidism, generalized decalcification and bone cysts, together with hypercalcemia, hypophosphatemia and a marked negative calcium and phosphorus due to loss in the urine are characteristic findings.[16] The blood phosphatase activity is consistently elevated in hyperparathyroidism with extensive skeletal changes, but rarely exceeds 10 times the normal maximum. In remission, however, whether the result of surgical removal of parathyroid tumors or occurring spontaneously in the course of the disease, recalcification, particularly of large cystic areas, may produce a roentgenographic picture somewhat similar to Paget's disease. In this stage, moreover, the serum calcium and phosphorus are usually normal, the calcium and phosphorus balance is positive or within normal limits and the serum phosphatase may still be somewhat elevated.

The few cases of tertiary syphilis with bone involvement (commonly of the tibiæ and clavicles) seen at this hospital in the last 10 years did not present any serious problem in diagnosis. The radiologic features of proliferative luetic periostitis[17] differ markedly from those of Paget's disease. Only 7 of our cases of osteitis deformans had a positive Wassermann reaction in the blood and in 5 of these clinical manifestations of syphilis were present.

Melorheostosis[18] begins in younger individuals, is unilateral and usually involves the long bones of a single extremity, often including the hands. It is a form of osteosclerosis which produces an expansion with undulating contour of one aspect of the cortex. Involvement of the skull has not been described.

Three cases of leontiasis ossium were encountered.[19] The patients were less than 30 years of age and all stated that the deformity of the face had been present since childhood. The hyperostosis was confined to the facial bones in 2 instances, with encroachment upon the frontal bones and base of the skull in the third case. The remainder of the skeleton was not involved. The serum phosphatase was 2.8 and 3.5 Bodansky units per 100 cc. in the 2 cases investigated. The serum calcium and inorganic phosphorus were also normal.

Bowing of the tibiæ due to rickets acquired in childhood is readily distinguished from Paget's disease. Garrés' sclerosing osteomyelitis,[20] osteopetrosis,[21] hyperostotic meningiomas,[22] and cases of neurofibromatosis[23] or of yaws[24] with bone involvement may simulate superficially certain aspects of Paget's disease.

Management. The treatment of Paget's disease is symptomatic. Relief of pain by ultraviolet light, by administration of calcium, parathormone, viosterol and by acidotic salts such as ammonium chlorid has been reported.[25] Several of our patients had received one or more of these agents but in every instance without benefit or with transient and apparently subjective relief only. Beneficial effects have been reported also for arsenic,[2c] dried suprarenal extract by mouth[2d] and parenteral administration of extracts of adrenal cortex,[26] with which we have had no personal experience. The only unequivocal, although often temporary, relief of pain in our cases, apart from analgesics, was obtained in some patients by Roentgen therapy to the affected bones. In 30 cases treated with relatively small doses, the best results were obtained where the pain was localized to non-weight bearing bones. Headache and vertigo were helped in 4 cases by radiotherapy to the skull. In the evaluation of our results, as well as those reported by others, it should be kept in mind that spontaneous remissions of pain in Paget's disease are not uncommon.

Where unusual decalcification and muscle atrophy due to disuse had developed, high calcium diets with calcium and viosterol by mouth, together with carefully graduated exercises were instituted (see Case A. O.). Built-up shoes facilitated walking when limp resulted from shortening of one leg due to bowing. The selection of proper hearing appliances proved a boon when deafness was the presenting complaint.

Since spontaneous remission of pain and arrest of the process are not uncommon, this possibility should be held out to all patients. The probability of very slow extension of the disease or quiescence would appear to be greater when the elevation of blood phosphatase is inconsiderable.

Etiology. The prevailing opinion appears to be that Paget's disease is the result of some local disturbance in bone metabolism, the immediate cause of which is unknown. The preponderance of evidence, pathologic, clinical and biochemical, indicates that Paget's disease is not a generalized systemic disease, infectious or endocrine in nature. As in all previous reports, our cases did not show fever, cachexia, secondary anemia, leukocytosis or an increased erythrocyte sedimentation rate, where this was investigated, except when obviously due to coexisting pathology. Definite evidence of parathyroid overfunction was not observed in any case. Postmortem examination in 3 of our cases revealed parathyroid glands normal in size and histologic structure. There is no reason to consider syphilis or trauma as etiologic factors. The increase in phosphatase activity of the blood in osteitis deformans is probably a result and not the cause of the disease (Kay). The occurrence of Paget's disease in several members of the same family is exceptional and it is

doubtful that heredity plays a significant rôle in most cases. Neurotrophic and localized chronic inflammatory processes have been considered as etiologic factors. The frequent association of arteriosclerosis with Paget's disease has suggested that sclerosis of the nutrient arteries may be a factor in causation.[27] Pathologic demonstration is lacking, however. The lesions resulting from obliteration of nutrient arteries as observed clinically or experimentally do not resemble Paget bone, which is often conspicuously hyperemic in the presclerotic stage ("spongy hyperostosis," Wilks). The rarity of involvement of the small bones of the hands and feet, particularly exposed to occlusion of the peripheral circulation, would also seem to be inconsistent with this view.

Summary. 1. Observations on 104 cases of Paget's disease seen at the Presbyterian Hospital from 1915 to 1935, and 12 cases seen elsewhere are summarized. Osteitis deformans is among the more common primary bone diseases in patients over 30 years of age.

2. The diagnosis in all cases was based upon typical Roentgen-ray findings. Twenty-seven cases presented no symptoms or signs referable to Paget's disease, the lesions being discovered incidentally by Roentgen ray while examining other systems. In only one-third of the cases were the clinical findings sufficiently definite to warrant the diagnosis clinically. The large majority of cases were not advanced so far as to present the classic picture of osteitis deformans when first examined.

3. There was equal distribution of the sexes. With one exception, all patients were over 30 years of age. Familial incidence was recorded in 4 cases.

4. The incidence and characteristics of the initial and major subsequent symptoms and signs in this series of cases are outlined.

5. Five representative case histories are presented to show how widely the course of the disease may vary, depending in large part on the location, extent, stage and rate of development of the Paget lesions. In 2 cases, the clinical and radiologic changes over a 10-year observation period are contrasted.

6. The incidence of bone involvement, sites of predilection of early lesions in various bones and the nature of changes observed in follow-up studies, as shown by Roentgen ray, are discussed.

7. The serum calcium, inorganic phosphorus and phosphatase activity were determined in over 70 cases. The serum calcium and inorganic phosphorus were consistently normal in uncomplicated cases. With the exception of 1 early case, the serum phosphatase consistently exceeded 4 Bodansky units per 100 cc., reaching values over 100 Bodansky units in advanced cases. Our results favor the view that the blood phosphatase activity is roughly proportionate to the extensiveness and activity of the Paget lesions. The phosphatase values in any one case were usually remarkably

constant over long intervals. High blood phosphatase values are found in other bone diseases, particularly osteoplastic prostate metastases. In most instances, the radiologic diagnosis was obvious before the rise in blood phosphatase was striking.

8. The differentiation of Paget's disease from osteoplastic carcinoma metastases, hyperparathyroidism, bone syphilis, leontiasis ossium, melorheostosis and other conditions is briefly discussed.

9. The symptomatic treatment of osteitis deformans is considered, with particular reference to alleviation of pain by radiotherapy over the affected bones.

10. Various theories as to etiology are mentioned. Clinical or laboratory evidence for infection or endocrine disturbance was lacking in our cases. Postmortem examination in 3 of our cases revealed no gross or microscopic abnormalities of the parathyroid glands.

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A PREVIOUSLY UNDESCRIBED GRANULE WITHIN THE LYMPHOCYTE.

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In a recent study of the differential characteristics of blood cells when stained supravitally,[12] casual note was made of certain structures which appear in the cytoplasm of a significant and fairly constant percentage of the circulating lymphocytes. Further study of these bodies confirmed this original finding and suggested elaboration of their characteristics.

For a long time subsequent to the initial examination of blood with the microscope, lymphocytes were regarded as non-granular cells and classified as such by Ehrlich.[22] Schilling[28] and Virchow[31] have spoken of the lymphocyte as being a homogeneous globule. In 1902, Michaelis and Wolff[22] described the presence of certain granules within the spongioplasm of many lymphocytes. These were termed by Ferrata,[22] "plasmasomes," but have since been named "azure granules" as they take a bright red stain with the azure component of the Romanowsky dyes. They are not visible in the unstained state and are probably not stained by the supravital dyes.[27,4] Altmann in 1890, utilizing an acetic acid free fixative, observed the presence of certain cytoplasmic filaments which had previously been vaguely described in many different cells (Flemming, Maggi, etc.).[6] In 1899, Benda gave these structures the name "mitochondria" and they were further studied and established as normal constituents of the living cell by Schridde.[18,24] Additional investigation by Cowdry[5] has identified these structures as a cyto-

plasmic feature of the lymphocyte and has exhibited their specificity for the dye, Janus green. Sabin[27] and many others[8] have demonstrated the presence of certain bodies comprising the "segregation apparatus" of the lymphocyte. These are found in the viable cell only, vary in number, are moderately refractile, and are stained specifically with neutral red.[13]

Other than the three structures described, there has not been recorded any regularly appearing "granule" in the lymphocyte. The literature is, however, replete with descriptions of intra-cytoplasmic bodies; some of which appear solely in lymphocytes, whereas others are not specifically noted as occurring in these cells alone. Russell[20] observed acidophilic bodies within disintegrating plasma cells which finally were extruded as a result of rupture of the membrane. Hammar[21] in 1912 identified certain droplike inclusions of lipoid nature in the cytoplasm of the occasional lymphocyte.

Various authorities have commented upon the presence of small dark bodies located usually in the nuclear indentation[7,20,21] known as centrioles and stained with iron hematoxylin after the usual fixation. Large, so-called Foá-Kurloff[14] bodies have been demonstrated in the lymphocytes of older guinea-pigs, but apparently not in human blood. Cesaris-Demel[20] mentioned the presence of large, sudanophilic lipoid bodies within the cytoplasm of the component leukocytes of purulent material. Lewis and Lewis[17] noted the appearance within lymphocytes of tissue cultures of one or two small refractive granules, which did not change shape, size, or position and took the usual fat stains. These occurred predominantly in degenerating cells. Sabin,[27] Wiseman,[33] and others[18] have described refractile unstained particles within the hazy cytoplasmic remnant surrounding the nucleus of the effete lymphocyte. These entities are either disintegration products of the dying cells or normal structures which have lost their staining characteristics and have been modified morphologically in the course of cellular change.[29] Hu[15] has verified this latter phenomenon in mitochondria following damage to the cells containing them. Shipley[25] expressed the opinion that the presence of these vacuole-like structures represented the index of degenerative change. Auer[1] demonstrated the presence of peculiar bodies within the cytoplasm of large mononuclear cells in a case of acute leukemia following massive hemorrhage. These bodies appeared black at a certain focus but were highly refractile. They occurred but rarely in the small lymphocyte and varied in shape from globules to rods. Bohrod[3] described solid, hyalin bodies in 18% of all the white blood cells in a case of acute myelosis. Comparatively few were in lymphocytes and they were not visible with the oil immersion lens. Doehle[34] indicated certain bodies present in the leukocytes of fixed smears taken from patients with scarlet fever. They have since been

described in other conditions.[2] These structures are not visible in the wet preparation and evidently take nuclear stains. Despite the multiplicity of these cytoplasmic inclusions, each has its own fairly well defined characteristics which preclude error in interpretation.

Description. The globular particles I wish to describe have evidently not been noted previously as constant features of white blood corpuscles. They occur almost exclusively within lymphocytes.* Very rarely have structures with somewhat similar characteristics been observed in monocytes. They have not been identified in any of the other blood elements. These bodies are small, smoothly contoured spherules varying in size from a point (oil immersion) to about 0.5 μ in diameter. The average has a diameter of 0.25 μ. In general however, they fall into two size groups; one in which the diameter ranges from a point to 0.25 μ, and the other from 0.25 to 0.5 μ. In a series of 50 protocols the predominance of the smaller form was in a proportion of 2 to 1.

These bodies have been noted almost entirely in wet preparations. Only 3 times in 30 fixed smears stained with Wright's stain has the presence of granules resembling them been demonstrated. Two of these preparations were drawn from a patient with hemochromatosis and one from a case of infectious mononucleosis. The blood for these smears was drawn concomitantly with that for wet preparations all of which contained a significant number of granules. Alcohol fixation and staining with the Romanowsky dyes evidently obscured this element.

The spherules are markedly refractile, appear solid black at one focus and have a colorless glassy sheen at another in the unstained state. Ordinarily a single granule and much less often 2 or 3 are present in one lymphocyte. In several cases of chronic myelogenous and lymphatic leukemia and one undiagnosed splenomegaly with anemia in an infant there have been observed as many as 8 in a single cell, but never more. Only 1 or 2 cells among 200 to 400 lymphocytes counted in each of these patients displayed this number. The characteristics of the globular particles were exactly the same as those in the ordinary lymphocyte. They were all approximately the same size (0.3 μ). When two granules were present in a single cell, as occurred in about 30 to 40% of the spherule containing lymphocytes, one was more often much smaller than the other.

These intracellular inclusions are actively motile. In preparations examined promptly after withdrawal, their motility is most striking. They course about usually within the perinuclear zone, often under or over the nucleus, in a zig-zag fashion. Occasionally

* Dr. William Dameshek writes us that he has personally examined these preparations and that "there is unmistakably a rather opaque refractile granule in many of the lymphocytes."—[EDITORS.]

they obtrude toward the periphery of the cell but generally they remain quite close to the nucleus. As they approach the nuclear *Hof* they frequently impinge upon other less motile cytoplasmic structures (mitochondria and segregation apparatus) lending to these

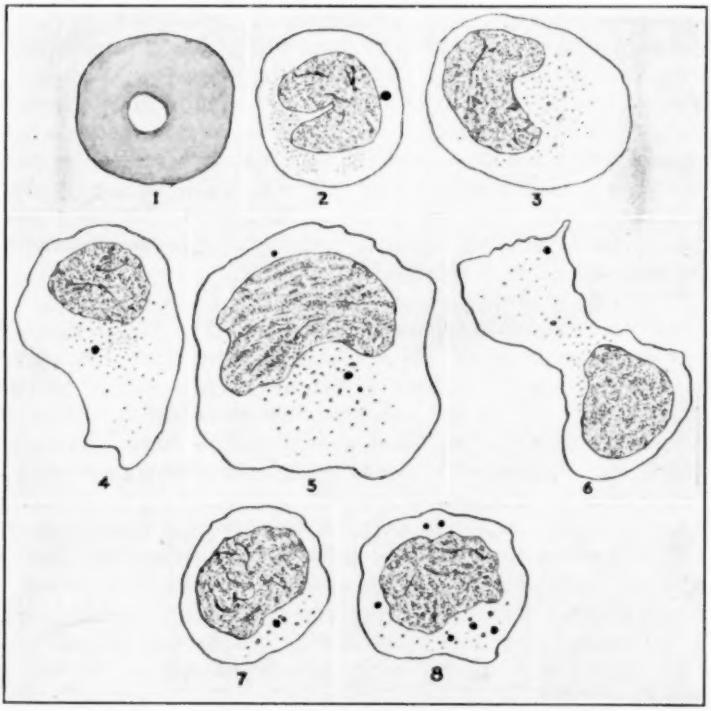

PLATE I.—All of these cells are unstained and are drawn from wet preparations of human blood. (1) This is a normal erythrocyte inserted for size contrast. (2) A small lymphocyte with a large refractile body opposite the indentation of the nucleus. The clumps of fine smudgy granules are probably mitochondria. (3) An intermediate lymphocyte with many fine and a few coarse, smudgy granules in the bay of the nucleus. There are no refractile bodies present. (4) A motile lymphocyte with a single, small refractile spherule which dragged along behind the nucleus. (5) A large lymphocyte containing three refractile bodies. Two of them are large and one is point-sized. (6) A rapidly motile lymphocyte with two refractile bodies, one of which remained close to the nucleus whereas the other bobbed about in the dragging tail of the cell. (7) A small lymphocyte in a preparation standing for 4 hours. The two refractile bodies, of unequal size, have come to lie together, close to the flattened portion of the nucleus. (8) A lymphocyte observed in the blood of an infant with anemia and splenomegaly. There are six refractile bodies present.

added impetus and receiving in return retardation and deflection of their momentum and course.[6,17] As has been noted, the motility of the other visible cytoplasmic elements was neither as rapid nor extensive as that of the refractile bodies.

The wandering spherule often ceased movement momentarily, vibrated in a rotatory fashion about a single point, and then resumed its course again. Frequently this pause was prolonged and even vibration ceased for as long as 30 minutes. Occasionally vibration returned intermittently without any other movement of the granule. Eventually the progressive motility usually returned. The impression garnered from continued observation was that the general course tended to be toward and away from the region of the centrosphere in the indentation of the nucleus. Ultimately, as the preparation aged or some toxic dye (Janus green, etc.)[4,11] was added to it, the refractile body came to lie at this central point in the nuclear bay and remained here constantly without visible motility or change until the cell disintegrated in 72 to 96 hours. At this time the granule, often indistinguishable from the products of cellular degradation, came to lie in the surrounding medium.

When two refractile granules were present in the same cell, the smaller one was usually found on the same side of the nucleus as its indentation and did not often migrate for any great distance from this point. Its movement was of the same type as that of the larger body in that it, too, had a zig-zag course as well as a vibratory character, the latter being the more frequently evident. The smaller granule also seemed to be controlled by some force exerted by the centrosphere for it appeared to jog about much like a rubber ball on an elastic band. Occasionally, the two bodies remained vibrating in a jerky fashion at opposite sides of the nucleus and then slid rapidly toward each other to meet in the nuclear bay without any evident jolt. Ultimately, as the preparation became older ($1\frac{1}{2}$ to 4 hours), the two came to lie proximate to each other in the vicinity of the centrosphere where they remained motionless. In this state they closely resembled the centrioles as illustrated by Cowdry[7] and Maximow[20,21] save for their unequal size.

The lymphocytes containing these bodies were themselves often actively motile when unstained or stained with neutral red alone. When the temperature of the warm box was raised to 39 or 40° C. the cells assumed their characteristic motility[15, 19, 23] and the granule was observed bobbing along passively in the streaming tail of cytoplasm. The spherule retained, however, its own relative motility for when the cell became static the refractive particle again resumed its own wanderings. Rarely the body was observed in the thin film of cytoplasm ahead of or underlying the moving nucleus but it rapidly slipped to the rear of the cell.

The refractile globules were not present in all lymphocytes. In a series of 120 wet preparations, both unstained and supravitally stained, viewed in a warm box at body temperature, they were present in an average of 34% of all lymphocytes. Fifty to 150 lymphocytes were counted in each specimen. The range extended

from 6 to 55%. In the great majority of these preparations the refractile granule bearing lymphocytes averaged 20 to 45% of the total lymphocytes counted. In a series of counts done upon 30 normal individuals an average of 39% of the lymphocytes contained one or two bodies. In 16 patients with some pathologic process which might conceivably influence the lymphopoietic system (tuberculosis, lymphatic leukemia, Hodgkin's disease),[10] 34% of the lymphocytes contained the granule. In a mixed series of patients suffering from all types of disease (rheumatic fever, pneumonia, diabetes mellitus, heart failure, trichinosis, etc.) the percentage of lymphocytes bearing the body closely approximated the mean of all the cases examined (36%). Only in infectious mononucleosis (1 case) was the percentage observed to remain persistently low (6 to 13%). In 10 individuals upon whom counts were done on 4 successive days the proportion of granule bearing cells was noted to remain remarkably constant in each person from day to day. The deviation was no more than 2 to 5%.

The globules were present more often in the small lymphocytes than in the large and intermediate forms.[8,9] They were more common in the mature and older lymphocytes whereas the young and immature forms contained them infrequently. The criteria of Hu and Wiseman[15,32,33] were utilized in the estimation of the age of the cells. Plasma cells contained the bodies in less than 3% of those identified. In the effete lymphocytes it is often impossible to distinguish the bodies from the products of disintegration present.

When observed with the polarizing microscope the granules were not doubly refractile. In preparations treated with 0.5% acetic acid they became darker, retained their form and contour, but lost much of their refractibility. They were entirely obscured by methyl and ethyl alcohol, and could not be recognized when the smear had been fixed by drying. In the wet preparation they were unchanged in appearance when subjected to temperatures ranging from 15° to 45° C. Motility was retarded with lowering of the temperature. Neutral red[11] imparted to them a dark mahogany hue but they did not appear to be stained by methylene blue, eosin, azure, Sudan III, osmic acid, Janus green, Bismarck brown, or iodin. Owing to the refractibility of the particles it was almost impossible to determine conclusively whether or not they were stained in any slight degree by these substances.

Comment. The significance of these refractile globules is not recognized. It is possible that they are products of cellular disintegration. Their predominance in the older lymphocyte suggests this to a certain extent. Their presence in the actively motile lymphocyte is somewhat unfavorable to this point of view, particularly since the continued activity and failure of the nucleus to become stained with neutral red is significant of the cell's viabil-

ity.[27] Furthermore, the globules are present in no greater proportion of the cells in the long standing (2 to 4 hours) than in the fresh preparations; nor is there any perceptible decrease in their numbers after 24 hours. On the other hand, with prolonged contact with a somewhat concentrated solution of neutral red, the lymphocyte will be damaged, motility will cease, and the nucleus will begin to take the stain.[4,27] At this time the movement of the refractile body will rapidly subside even though Brownian movement is initiated in other cytoplasmic particles. Likewise, the application of Janus green, which is rather toxic to intracellular activity,[30] produces rapid cessation of the granular motility and stasis within the *Hof* of the nucleus even before the mitochondria are fully stained. In view of these facts, therefore, it is readily conceivable that the globule is a natural component of the extra-nuclear substance of the lymphocyte and as such responds in a parallel fashion to external stimuli.

The failure of the particle to be stained by either osmic acid or Sudan III and its inability to exhibit doubly refractile qualities are points unfavorable to the belief that it is lipoid in nature.

As has been stated, the appearance of the granules after they have become static in the center of the nuclear indentation is very similar to that described by many as the centriolar apparatus.[7,20,21] The presence of one, three, or more of these in a mature, non-dividing, mononuclear cell rather disproves this possibility. In cells observed dividing amitotically in the wet blood spread, the globule remained passively wherever it happened to lie and exhibited little disturbance as the result of separation. One daughter cell contained the body, the other did not. That the granule is strongly influenced by centrosomal activity, however, cannot be disputed, since its movement apparently centers about this structure and it ultimately comes to lie in its immediate vicinity.

Failure to distinguish the refractile spherules from the other previously noted structures within the normal lymphocyte is remote. Lawrence and Todd[16] have described the appearance of the neutral red staining bodies as "refractile blackish red." These, however, usually number 2 to 25 per cell and their red glint when stained makes them sufficiently distinctive to one familiar with the supravital technique.[8,9,27] Sabin has noted, further, that their index of refraction is similar to that of the cytoplasm and they are observed therefore with difficulty in the unstained state.[26] Prigosen has described the presence of neutral red staining bodies which he claimed might not take the dye immediately.[25] His illustrations lend no weight to the possibility that they are similar to the globule I have demonstrated. He enumerated four cytoplasmic granules of the lymphocyte, only one of which was not stained by neutral red or Janus green and this was a lipoid droplet. Mitochondria,

by reason of their smudgy, non-refractile character, their number, size, rod shape, and specificity for Janus green may not readily be mistaken for the refractile body.[5,8,9] Wiseman has noted the presence, occasionally, of non-staining refractile granules which have been found, however, only in those cells which do not contain mitochondria.[29,32,33] Furthermore, he has demonstrated as many as 30 in a single large lymphocyte. Finally, the azure granule of Wolff and Michaelis[4,27] is not visible in the unstained state and is probably not stained by the supravital dyes.

In only 3 cases of 130 examined was there any marked deviation from the average percentage of granule bearing lymphocytes observed. As has been previously noted in 8 counts done upon a patient with infectious mononucleosis wherein 57 to 130 lymphocytes were counted in each preparation only 6 to 13% of them contained the refractile body. The absolute number of lymphocytes containing these bodies was also reduced although not to as great a degree. In 5 counts done upon 2 patients with myelogenous leukemia in each of which 200 to 400 leukocytes were counted, only 2 to 9 lymphocytes were observed. Of these, 0 to 50% contained refractile bodies. In these cases, however, the absolute number of such lymphocytes was not always reduced since the total leukocyte count varied from 200,000 to 500,000 per c.mm.

In a series of 12 individuals upon whom serial counts were done for 72 hours following intracutaneous injection of tuberculin no significant change in the percentage of granule bearing lymphocytes was noted regardless of the extent of the local or systemic reaction.

Summary and Conclusion. Description is given of the presence of a motile, refractile globule which is normally present in a fairly constant percentage of the lymphocytes of peripheral blood observed in wet preparations. The bodies vary in size from a point to about 0.5 μ in diameter and appear in approximately 34% of the circulating lymphocytes. They occur for the most part in normal lymphocytes but have been noted in pathologic cells as well. The numbers of granule bearing lymphocytes remain quite constant in the same individual from day to day. They do not appear spontaneously or disappear in the standing blood spread. One or two are observed in a cell, rarely more. The spherule is neither mitochondrial nor one of the neutral red staining bodies previously described as existing in lymphocytes. It is probably neither of a lipoid nature nor a portion of the centrosphere. It appears to be a hitherto undescribed constituent of the cytoplasm of the lymphocyte.

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BARTONELLA CANIS INFECTION IN RELATION TO SECONDARY ANEMIA AND THE ASSOCIATED UNDERLYING LESIONS.

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In 1928, Kikuth[1] described an organism associated with a peculiar progressive cyclical anemia in splenectomized dogs. Close similarity to the Bartonella group, as regards biologic and morphologic characteristics together with the almost identical associated blood dyscrasia, induced him to designate this organism as Bartonella

* Thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Medical Science (D.Sc.(Med.)) for graduate work in Pathology.

canis. "These organisms," he says in his original report, "remind one partly of the Bartonella bacilliformis (human) and partly of the Bartonella muris." He believed them to be causative of the accompanying anemia, acting in the capacity of a parasite in the dog's red corpuscles, in or on which they were found. With Giemsa's stain these parasites showed up well resembling either cocci or bacilli. Their morphology was not, however, constant, being changeable into manifold shapes and occupying varying positions in relation to each other.

Splenectomized dogs sicken regularly if infected with Bartonella, the infection assuming either an acute or a chronic course. Death has occasionally been observed at the height of the acute infection, but recovery is the usual outcome in the chronic type. Normal non-splenectomized dogs, if injected with Bartonella, develop an abortive illness, passing off into a latent infection, which may occasionally be activated by splenectomy. Kikuth failed in numerous attempts to grow the organism on various types of culture media. He mentions therapeutic doses of neosalvarsan as having excellent curative action.

In 1909, Barton[2] had suggested that the bacilliform bodies, found in the blood of human beings suffering from Peruvian Oroya fever, were causative of that disease. Strong[3] and his associates, in their report of the first expedition to South America, speak of them as protozoa and suggested the term "Bartonella." Noguchi,[4] in studying a fatal case of Oroya fever, had the fortune to isolate the parasite in pure culture and with the same culture produce characteristic disease symptoms in animals. In further experiments Noguchi[4] found similar Bartonella-like bodies in the blood of a splenectomized rat. Lauda[5] gives us a detailed account of the anemia in splenectomized rats, in which bodies occurred in the erythrocytes strikingly similar to those seen by Noguchi.

Regendanz and Reichenow,[6] following up the work of Kikuth, give us a rather careful and detailed descriptive picture of this polymorphous parasite. They regard the differentiation into rod-like and cocci forms as not particularly well chosen because the rods are for the most part found to consist of beaded little bodies (cocci); naturally, therefore, not individual entities but rather chains of parasites. In their opinion the basic form of Bartonella canis is the coccus form and all complicated formations occurring in the red corpuscles are simply colony growths.

Within the past year various papers have appeared in which the nature and course of the anemia associated with Bartonella bodies have been recorded by American workers, notably Knutti and Hawkins,[7] Rhoads and Miller.[8] Knutti and Hawkins,[7] working with splenectomized bile fistula dogs, noted periods of bile pigment overproduction and anemia occurring spontaneously in conjunction

with the presence of Bartonella bodies in the blood. Prior to these observations Queen, Hawkins and Whipple,[9] also working with splenectomized bile fistula dogs, were well acquainted with the cyclical bile pigment overproduction, anemia and intoxication arising in these dogs. They even went as far as to determine the daily quantitative overproduction of bile pigment during these cyclical periods, which in some instances reached 8 to 10 times control values.* Thus in one cycle of pigment overproduction an average 24-hour output of 581 mg. of bile pigment was recorded. On one day during this cycle an output of 878 mg. of bile pigment was observed, or more than ten times the control level (78 mg. per day). They had been at a loss to satisfactorily explain these phenomena and failed to recognize Bartonella bodies in the blood at that time, presumably no search having been made. Thus in the absence of a demonstrable infection, it had been assumed that the periods of bile pigment surplus and anemia were of physiologic origin, related to a lack of spleen and bile constituents. With the finding of the Bartonella canis in these blood dyscrasias, the situation seemed to clarify and the evidence pointed to that organism as the probable etiologic factor.

Various investigators have observed periods of anemia in splenectomized dogs. Krumbhaar[10] looks upon the temporary anemia as a physiologic response to the loss of the spleen. He believes that the normal spleen in addition to its hemolytic function has also a stimulating effect on the red blood-cell formation, citing as supporting evidence the fact that anemia follows its removal. He regards this anemia as due to a loss with the spleen of a property which aids erythrocytes formation, such as conservation of the iron of broken-down red corpuscles. This function is in time taken over, at least in large part, by other members of the reticuloendothelial system, accounting for the temporary character of the postsplenectomy anemia. Furthermore, normal spleen extract has a stimulating, not an inhibitory, action on erythropoiesis in the bone marrow.

The question now arises, in the light of our more recent knowledge, whether this temporary postsplenectomy anemia observed in the past could possibly have been the result of an unrecognized latent Bartonella infection, activated by splenectomy. Against this likelihood stands an array of convincing evidence. The majority of investigators are in agreement, that spontaneous latent infection with Bartonella canis does not become activated in normal dogs with splenectomy alone. A few workers, however, cite such to be the case in an occasional simple splenectomized dog. I have, in the course of my experiments, observed 2 dogs for 60 days following simple splenectomy, during which time there was no evidence of Bartonella infection or Bartonella bodies in the blood, yet an anemia developed similar in character and degree to that described by

Krumbhaar[10] and others[11] as postsplenectomy anemia. A transient, non-infectious, postsplenectomy anemia, therefore, seems to be the most likely explanation.

TABLE 1.—CHANGES IN THE ERYTHROCYTE COUNT AND HEMOGLOBIN CONTENT OCCURRING IN DOGS WITHOUT BARTONELLA INFECTION AFTER SIMPLE SPLENECTOMY, OBSERVED FOR A PERIOD OF 60 DAYS.

Dog. 269.			Dog. 312.		
After splenectomy, time in days.	R. B. C.	Hemoglobin.	After splenectomy, time in days.	R. B. C.	Hemoglobin.
*	5.81	94	*	6.10	80
3	5.20	84	3	5.80	70
5	4.90	80	5	5.75	75
8	5.40	80	8	5.50	68
12	5.20	78	12	5.50	60
18	5.20	84	18	5.00	58
24	5.00	75	24	5.00	55
30	4.80	67	30	4.90	55
31	**4.80**	**63**	36	**3.30**	**46**
42	5.00	67	42	3.90	46
48	4.85	61	48	4.00	48
54	4.90	77	54	4.40	52
60	5.00	84	60	4.60	55

* Preliminary count and estimation.

In both of these dogs a secondary anemia gradually developed following the operation. The anemia in both cases was most severe during the fifth week. Then with a gradual improvement, the blood picture tended to approach the pre-operative level. As may be readily seen from the table, the latter had not been attained in either dog at the end of the 60-day period of observation. Krumbhaar[10] regards the average length of time for complete restoration of the blood picture to normal as 3 to 4 months. The hemoglobin decrease occurs somewhat sooner and is also more outstanding than the red cell drop, and as improvement occurs the increase in hemoglobin tends to lag notably behind the erythrocyte increase.

Either splenectomized bile fistula dogs (Knutti and Hawkins[7]), or simple splenectomized dogs, fed on deficiency diets producing black tongue (Rhoads and Miller[8]), appear to show regular spontaneous involvement with Bartonella canis and anemia. The authors are insistent that in both experiments simple splenectomy will not bring about Bartonella infection. Krumbhaar,[10] in his extensive studies of changes produced in the blood by splenectomy, failed to note a marked degree of anemia or the presence of Bartonella bodies, even though the spreads have recently been reëxamined with this point in view. Being acquainted with the infectious anemia (Bartonella) lit up by splenectomy in rats and reported by Lauda,[12] he was especially on the lookout for these parasites. It may be said that simple postsplenectomy anemia does not attain the severity of that observed complicated by Bartonella infection. Furthermore, the isolated simple splenectomy cases reported in

earlier medical literature as developing typical Bartonella canis-like anemia, may in all probability be related to some such diet deficiency complication referred to above.

Method. The work was begun by transmitting the Bartonella infection to a simple splenectomized dog by the injection of 5 cc. of Bartonella blood obtained through the kindness of Dr. G. H. Whipple, to whom I am also indebted for valuable suggestions in pursuing the problem. The 5 dogs on which this study was based were infected from this dog as the original source. One dog (No. 269) was used as a special control, in addition to the earlier simple splenectomies done in this department. Blood smears were taken at almost daily intervals and examined for the organism, using the Giemsa method of staining. Frequent red cell counts and hemoglobin determinations were made at weekly or lesser periods. The more frequent blood examinations were made at those periodic intervals in the course of the infection when the blood smears became positive for the Bartonella bodies. By this method, sudden transitions in the blood could be more easily detected and the relationship of the appearance of the organism to the developing anemia better evaluated.

Infection Cycle of Dogs With Bartonella Infection. In general, the course of the infection developing in our dogs, excluding minor variations, corresponded rather closely to that reported by other earlier investigators, notably Regendanz and Reichenow.[6] The incubation period after injection varied from 7 to as much as 15 days, a somewhat longer period than that usually reported (3 to 5 days). This period was followed by the appearance in the blood stream of the Bartonella organism at first few in number, then increasing rapidly for several days only to decrease and disappear suddenly. An interval of freedom from the organism, variable in the different dogs from several days to a week or more, but present in all, occurred before recurrence with rapid proliferation was again observed in the blood smears. As regards the general duration of the subsequent intervals and the renewed attacks which followed periodically, one upon another, it may be said that it varied throughout the course of the infection. The shortest intervals and the longest attacks took place at the time that the infection course seemed to be at its peak, as judged by the number of organisms present and the marked blood destruction with its attendant severe anemia. By attack, one refers to that time interval during which the organisms were numerously present in the red corpuscles and detectable by the microscope.

Thus Dog 24 (Fig. 2) showed a rather regular course at first, for a long time running attacks of 8 to 10 days' duration with intervals averaging 10 days. After the fourth attack, which was preceded by a shorter interval of 4 days, an irregular course developed until the attacks ceased altogether. A different course was observed in Dog 25 (Fig. 3), in which at the beginning long lasting intervals occurred, which were separated only by short attacks, and later two long attacks of 10 days' duration were followed by an attack

FIG. 1.—Blood smear obtained from Dog 24 at the peak of anemia. Various forms of Bartonella bodies are clearly demonstrated, *viz.*, single spherical forms, long beaded rodlike forms, simple rod forms and complicated formations. Giemsa stain. × 1600.

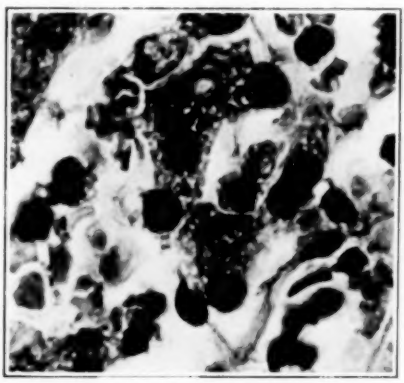

FIG. 7.—Photomicrograph of liver from Dog 25. Numerous Kupffer cells are present. These appear for the most part swollen and block the lumen of the intralobular capillaries. × 1050.

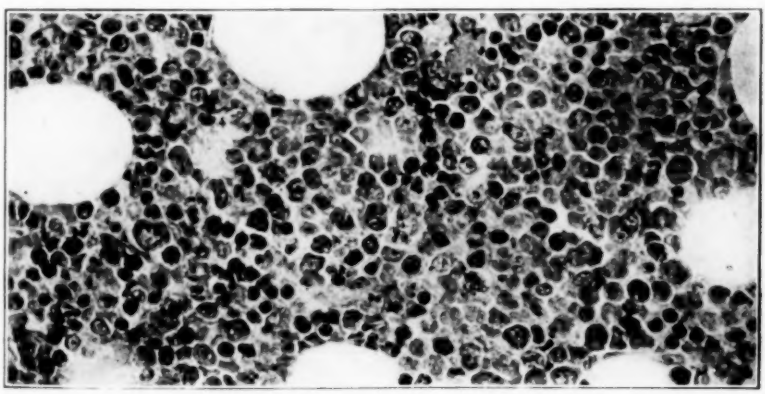

FIG. 8.—Photomicrograph of bone marrow from Dog 25. This section was taken from the proximal end of the femur. There is a marked hyperplasia of all the elements of the bone marrow. Azure II eosin stain. × 436.

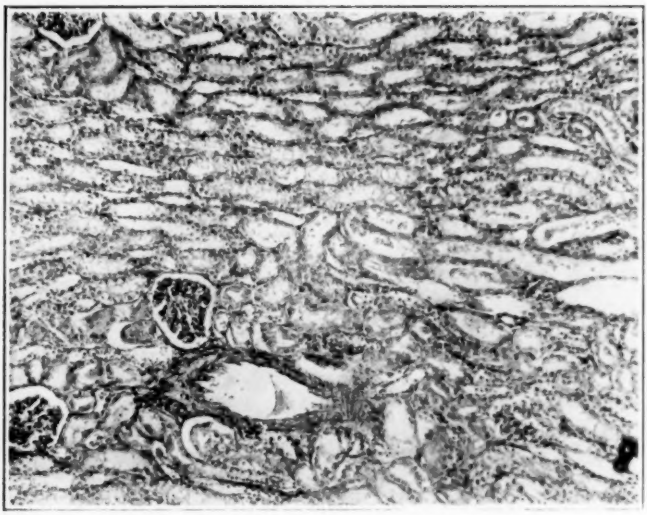

FIG. 9.—Photomicrograph of kidney from Dog 1052 showing extensive tubular degeneration. × 102.

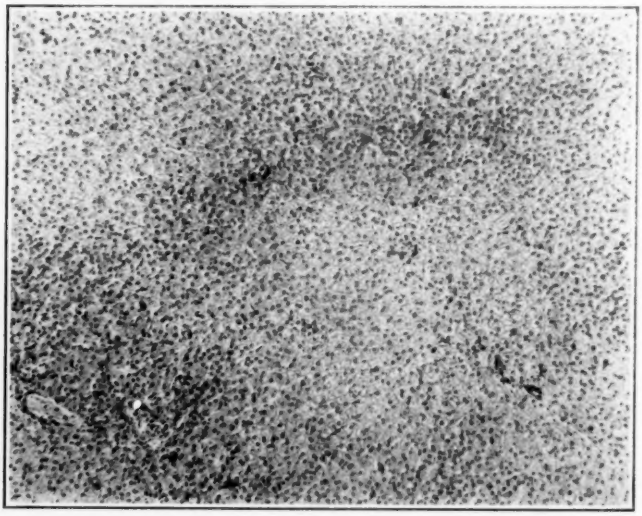

FIG. 10.—Photomicrograph of liver from Dog 24, showing focal necrosis confined principally to the center of the lobules. In areas fat droplets appear in the cytoplasm. Kupffer cells are small and normal in appearance. Small collections of lymphocytes are encountered in the periportal areas. × 102.

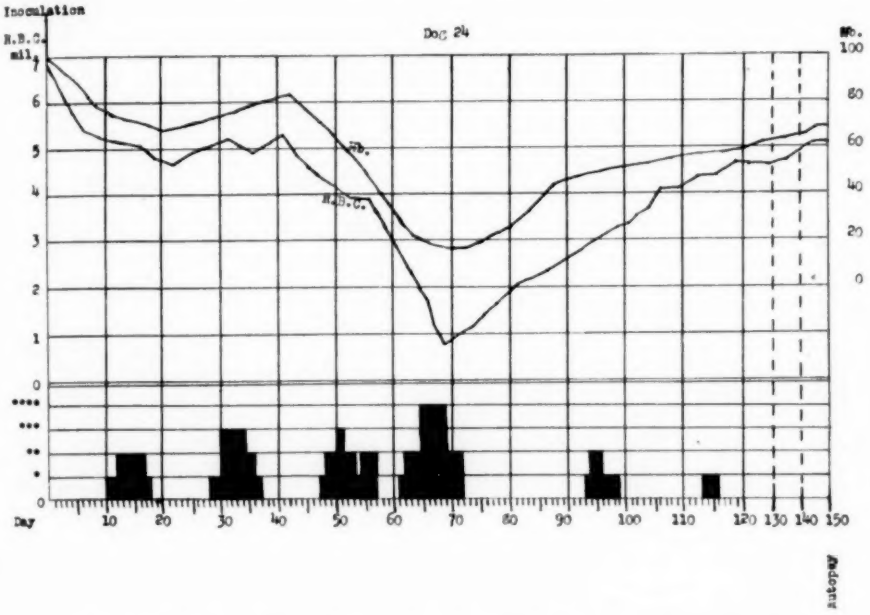

FIG. 2.—Dog 24. Bartonella incidence and anemia in injected splenectomized dogs. **** Preponderance of blood cells containing Bartonella. *** Several red cells with Bartonella per field (oil immersion). ** Average one organism per field (oil immersion). * Occasional organism in smear.

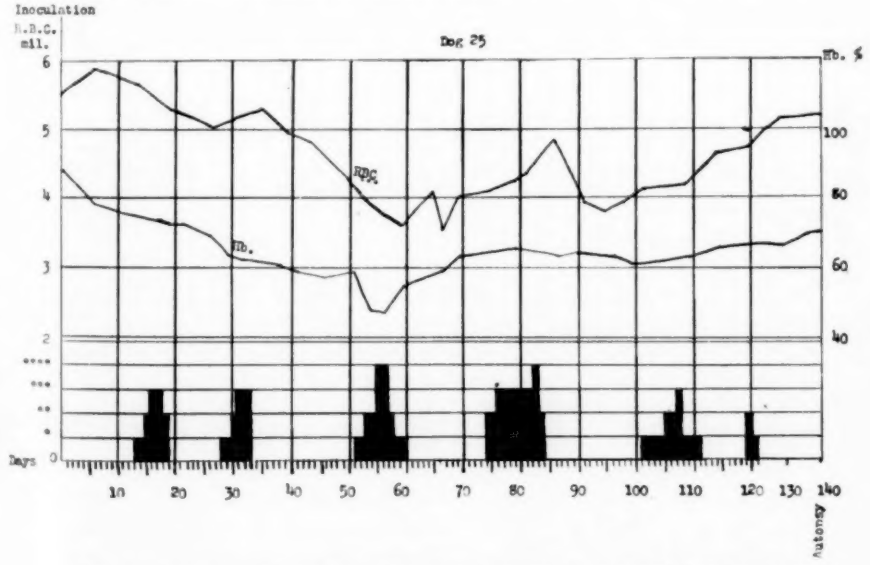

FIG. 3.—Dog 25. Bartonella incidence and anemia in injected splenectomized dogs. ****Preponderance of blood cells containing Bartonella. *** Several red cells with Bartonella per field (oil immersion). ** Average one organism per field (oil immersion). * Occasional organism in smear.

of 2 days, terminating the course of the infection. In Dog 268 (Fig. 4) the following course occurred: After two short-lived attacks lasting 5 days and separated by an interval of 7 days, there followed a 14-day interval. The new attack lasted 18 days, whereupon an 11-day interval occurred. Then followed one attack of 3 days after which the smears remained negative. In this dog the blood picture failed to return to a normal level 2 months after the last organisms appeared. In all other dogs after the infection sub-

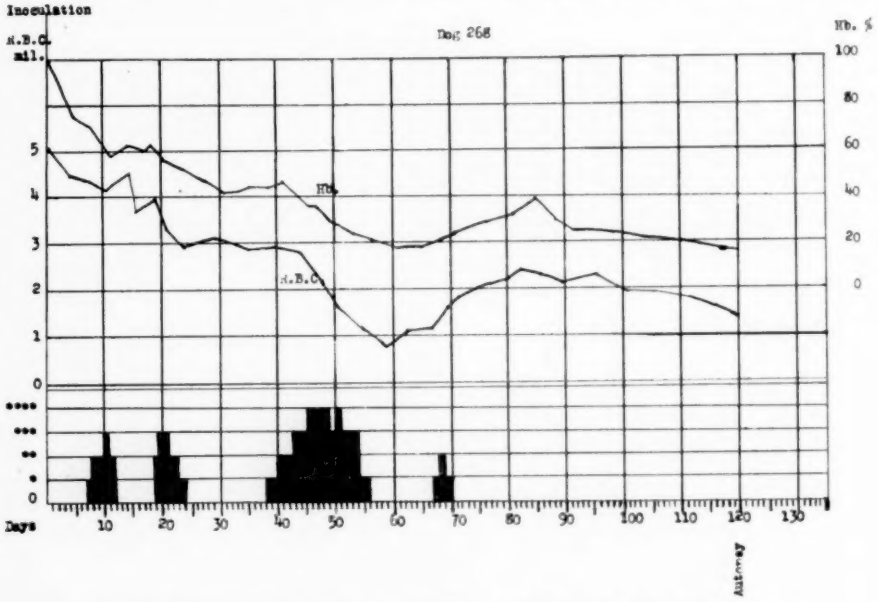

FIG. 4.—Dog 268. Bartonella incidence and anemia in injected splenectomized dogs. ****Preponderance of blood cells containing Bartonella. *** Several red cells with Bartonella per field (oil immersion). ** Average one organism per field (oil immersion). * Occasional organism in smear.

sided, the blood reached or tended toward normal levels. One is inclined to believe that an abdominal wall sinus in Dog 268 draining at intervals throughout the latter part of the Bartonella and post-Bartonella infection period accounted for the severe persistent anemic blood picture. Interesting was the course of Dog 312 (Fig. 5) in that only two attacks occurred. The organisms appeared first in the smears, 7 days after injection with Bartonella positive blood and again after an interval of 9 days. Both attacks lasted 5 days and in neither instance were the organisms very numerous. The infection course of Dog 1052 (Fig. 6) was cut short by sacrificing the animal in the early stage of the infection, 10 days after the first appearance of the Bartonella and while the blood smears were

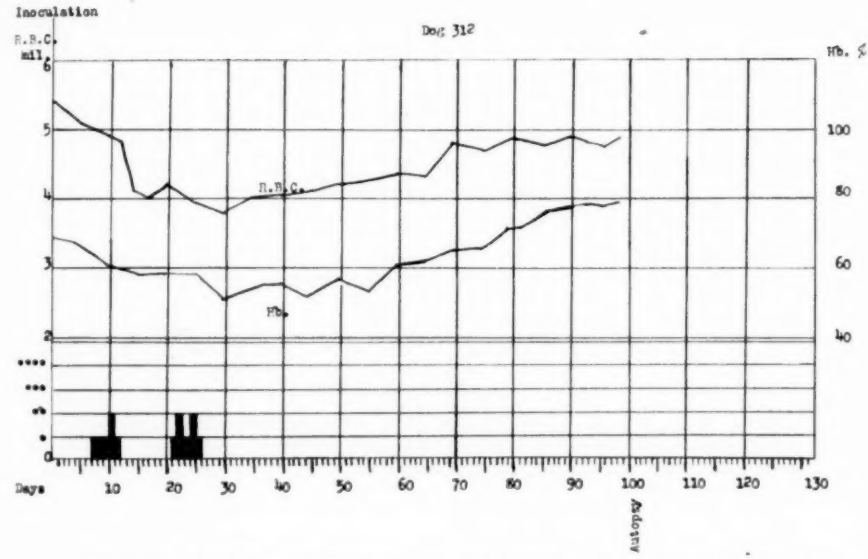

FIG. 5.—Dog 312. Bartonella incidence and anemia in injected splenectomized dogs. ****Preponderance of blood cells containing Bartonella. *** Several red cells with Bartonella per field (oil immersion). ** Average one organism per field (oil immersion). * Occasional organism in smear.

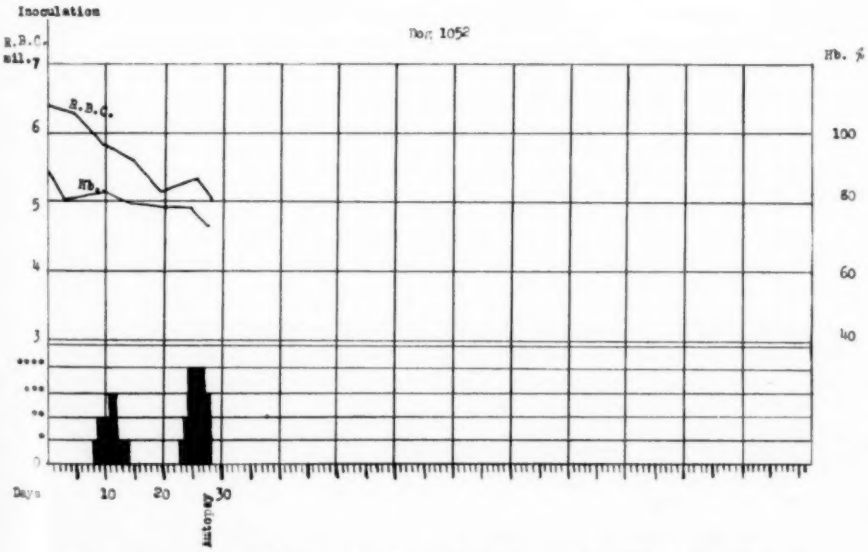

FIG. 6.—Dog 1052. Bartonella incidence and anemia in injected splenectomized dogs.

showing organisms in great numbers. This procedure was adopted in order to determine and study the histologic changes occurring in the early stage of the Bartonella infection. Blood regeneration, as judged by the numerous immature forms (macroblasts, normoblasts) and the high reticulocyte count in the smears, was fairly active.

Effects of Bartonella Canis on the Organism. The outstanding feature of the Bartonella infection, observed in the dogs as a group, was the severe type of anemia encountered and associated with an extreme degree of general emaciation and physical weakness. It has been said,[6] that Bartonella canis anemia is of lesser intensity than the infection in man with Bartonella bacilliformis (Oroya fever) and the infection in the splenectomized rat with Bartonella muris. One is rather reluctant, however, to fully subscribe to this statement, for 2 of our dogs (Nos. 24 and 268) developed at the height of their infection an anemia of extreme severity in which the red corpuscles dropped to 910,000 and 750,000 per c.mm. respectively. The hemoglobin determination in both dogs read less than 3 gm. per 100 cc. At the time the above blood findings were recorded, these dogs showed extreme body emaciation and such physical weakness that the exertion of a slow walk over a short distance gave way to a faltering gait and the development of severe dyspnea. In Dog 268 life was despaired of. Evidence of blood regeneration, however, went hand in hand with blood destruction and one was immediately struck by the large number of immature polychromatic and nucleated red cells occurring simultaneously with the degenerated forms. The reticulocyte count was noted as high as 30%, and undoubtedly reached higher levels in some cases. This condition existed not only at the height of the infection and after development of a profound anemia, but shortly after the first appearance of the organism in the blood smears, immature erythrocytes sprang into evidence. During the peak of the infection organisms appeared almost continuously in the blood stream, without interruption by a Bartonella free interval. Finally, after the infection began to wane, the blood (except in Dog 268) rapidly approached normal levels. The color index was in general below 1. Our animals recovered immediately as soon as the course of the infection changed for the better, namely when instead of long lasting attacks, intervals of longer duration appeared. No fatality occurred in our dogs. Also in subsequent attacks of long duration, there developed in these dogs decrease of hemoglobin and red cell count, which rose again during the interval when the Bartonella were not able to be found microscopically.

Autopsy Reports. All dogs used in these experiments had autopsies performed. Because of the loss of the spleen, which in mammals contains the bulk of the reticuloendothelial system, and influenced by the concept of reticuloendothelial organ interdependence, the histology of the lymph nodes, bone marrow, liver, lungs and kidneys were chiefly studied. The

dogs were killed with an overdose of chloroform and immediately sectioned. It might be mentioned that in all cases search was made for accessory spleens, but none were found. One dog (No. 1052) was autopsied at an early period of infection; another (No. 25) late in the infection period, while the remaining dogs (Nos. 24, 268, 312) were sectioned at various intervals after the last appearance of organisms in the blood smears. One splenectomized dog (No. 269) was used as a control and autopsied 160 days after splenectomy. A routine Zenker formol fixation, paraffin embedding and hemotoxylin and eosin stains was used. In the case of the lymph nodes and bone marrow special staining with eosin azure II was employed. Detailed protocols have been omitted.

Dog 1052. Autopsy in the early stage of the infection; 21 days after the first appearance of the organism and while the blood smears were showing the Bartonella bodies in great numbers. The dog was beginning to show emaciation and physical weakness with marked wasting of the subcutaneous fat. A light bile discoloration marked the wasted fat. The blood was thin and watery. The lungs were collapsed, the anterior surfaces being pale and the posterior areas more of a dark red color. No areas of consolidation were encountered. On section a mild degree of edema was noted. Bronchial lymph nodes were only slightly enlarged. The heart was dilated and the myocardium pale.

The former bed of the spleen was represented by a mass of fibrous adhesions. The liver was of normal size, soft, and light brownish yellow. The lobular markings were not clearly distinguishable. Scattered widely through the liver were seen focal areas of necrosis. Both kidneys were of normal size. On section the cut surfaces appeared pale and mild degenerative changes were seen in the cortex and medulla. The individual structures outlined dimly and the cut surfaces appeared swollen. Adrenals were soft but otherwise of normal appearance. Mesentery and retroperitoneal lymph nodes were slightly enlarged, soft and swollen. Bone marrow of ribs, sternum and proximal ends of the femur and humerus was red and gelatinous. For histologic study see next section.

Dog 25. Autopsy late in the infectious period several days after the last appearance of organisms in the smears and 144 days after injection with positive Bartonella blood. The dog was in a moderately well-nourished condition, having shown a marked improvement in physical strength from that seen earlier in the course of the infection.

Both lungs and pleural cavities and the heart appeared to be normal. Paratracheal and bronchial lymph nodes were slightly enlarged and darky pigmented. The liver was dark brown, firm, with the external surfaces smooth, and the cut surfaces showing the lobules distinctly. The kidneys were pale, somewhat swollen and only faint focal suggestive areas of necrosis could be distinguished. Mesentery nodes in the upper abdomen were greatly enlarged. In the region of the celiac plexus these nodes formed a fused chained mass about 8 cm. in length. Isolated large nodes were also found. On section the nodes were soft, moist and of a pale fleshy color. Adrenal appeared normal. Bone marrow selected from the proximal ends of the humerus and femur was typically red and of a firm gelatinous character.

Dog 268. Autopsy on the 119th day after inoculation. This dog was in a weakened condition and failed to show improvement from a severe grade of anemia, in spite of the fact that organisms were not found in the blood on careful search during the 48 days prior to death. This persistent anemia was most probably associated with an abdominal wall sinus, draining intermittently during the last 10 weeks preceding the autopsy, due to persistent silk ligatures in the bed of the spleen. Organization of the granulation tissue was well advanced, and only small localized abscesses imme-

diately surrounding the silk ligatures were seen. Although the blood picture failed to improve, a marked gain in weight had been recorded since the terminal Bartonella attack.

Both pleural cavities and lungs were apparently normal. Bronchial and tracheal lymph nodes were slightly enlarged, firm and spotted with bluish-black pigment. The myocardium was pale. The liver was spotted with small grayish spots varying in size from that of a pin-head to that of a small pea. This was especially noted in the right lobe. Sections showed the same findings. Parenchyma appeared otherwise normal. Adrenals and kidneys were normal. Lymph nodes of the mesentery, especially of the duodenum and upper end of the ileum, were enlarged and tended to form fused masses. On section these nodes were soft and of a dull pink-grayish color. Bone marrow of the upper half of the humerus and femur was red, soft and jelly-like.

Dog 312. Autopsy 98 days after first injection. The animal was emaciated but for the past week a decided change for the better was observed as regards physical strength and weight gain.

The lungs were apparently normal. Bronchial and tracheal lymph nodes were palpably enlarged and of a firm flesh-like consistency. On section the cut surfaces were rather soft, moist and of a dull grayish-pink coloration. Heart was enlarged. The myocardium of the left ventricle was firm, the right flabby and dilated. Liver was slightly enlarged, firm in consistency, the external surfaces were smooth and the edges sharp. On section gray specks were noted scattered throughout the liver, but nothing further of a pathologic nature presented itself. Both kidneys were apparently normal. Retroperitoneal lymph nodes were variously enlarged some to the size of a small bean. On section these nodes showed a soft, moist pulpy parenchyma of yellow-pinkish coloration. Bone marrow taken from the upper humerus and femur was predominantly red, soft and gelatinous. Bone marrow of the sternum was also of the red type but rather scanty in amount.

Dog 24. Autopsy 90 days after the last appearance of the organisms in the blood smears. The dog was in an excellent physical condition and had completely recovered from the severe anemia and weakness present at the height of the infection. The lungs were apparently healthy throughout. The bronchial nodes were moderately enlarged and pigmented. The heart muscle was firm and of good tone. The liver, gall bladder and biliary tract, gastro-intestinal tract, adrenals and kidneys presented nothing abnormal.

Only a few fibrous adhesions marked the splenic bed. Mesentery lymph nodes, especially those confined to the upper abdomen, were enlarged and fused into long masses often approximating 6 cm. in length and 2 cm. in width. The individual nodes, although massed together, tended to remain discrete.

Bone marrow removed from the proximal ends of the humerus and femur was light pink, with scattered yellow areas of fat interspersed. The typical red variety of the dogs autopsied during the infective period was not in evidence.

Dog 269. Autopsy 160 days after simple splenectomy. The dog was not infected with Bartonella and was used as a control. We were especially anxious to observe both the macroscopic and microscopic changes which might occur with the loss of the spleen. Special search was made in the lymph nodes and other reticuloendothelial structures to determine whether demonstrable definite compensatory changes appeared. This dog had been injected with trypan blue a year previously, evidence of which could be plainly seen in the various tissues.

The lungs and heart were normal. Bronchial lymph nodes were only slightly enlarged, discrete and spotted heavily with a bluish-black pigment.

In the abdomen the omentum was the seat of marked bluish-black pigment deposit as were also the intestinal mesentery and to a minor degree the bowel wall. The liver was smooth, normal in size, firm and dark bluish-red. The same dark color prevailed on section. Gall bladder and ducts were normal. At the site of the splenic bed a smooth scar was found. No supernumerary spleens were found. The lymph nodes were only slightly enlarged and peppered with bluish black pigment deposits.

The adrenals and kidneys were normal in size; the surfaces, both external and cut, showing a faint bluish tinge against a dark red background.

Bone marrow removed from the proximal ends of the humerus and femur was a combination of the red and fatty varieties. The consistency was soft, pulpy in character and of a dull pink gray.

Histologic Examinations. In reporting on the histologic changes observed, the material examined is conveniently arranged in two groups: I. Tissues obtained during the active infection period or the acute anemia stage (Dogs 1052, 25, 268), and II, those from dogs autopsied some time after the infection had run its course (Dogs 312 and 24). Dog 268 is considered in Group I because, even though organisms were not detected in the blood for a long time, the animal had not recovered from the severe anemia.

Variations in individual dogs distinct from the group as a whole will be referred to specifically. Dog 269 (control) will be considered separately.

GROUP I. *Active Infection Period.* Microscopically, the liver cells show some granular and fatty degeneration, especially in the central portion of the lobules. The ordinary undifferentiated endothelial lining cells of the liver sinusoids are not affected. The Kupffer cells are present in great numbers and show marked phagocytic activity. They are for the most part enormously swollen and seem to block the lumen of the intralobular capillaries (Fig. 7). In some areas the Kupffer cells show such proliferation that accumulations encroach upon and compress the cords of liver cells. The phagocytic activity of the Kupffer cells can be readily judged from the granules of green waste pigment, engulfed erythrocytes in various stages of disintegration and hemosiderin granules in their protoplasm. The microscopic section suggests that large amounts of cellular débris circulate in the blood during the height of the infection, a factor undoubtedly accounting for the marked stimulation of phagocytic activity.

The liver cells from Dog 25 do not show the marked degree of degeneration seen in Dogs 1052 and 268. The Kupffer cells in Dog 25, although not present in enormous numbers, are nevertheless abundant, and represent phagocytic activity and hyperplasia of the endothelial elements as occurring late in the dog's infectious period. As the blood picture at this stage is slowly approaching a normal level, these histiocytes are approaching their resting state. In this dog we also find small periportal foci consisting of small lymphocytes with reticuloendothelial elements in the background. These are probably the result of lymphoblastic hyperplasia rather than an expression of inflammation, for newly formed collagenous fibers and other proliferative fixed connective tissue changes characteristic of chronic inflammation are not in evidence.

In Dog 268 a diffuse exudate is also observed in the liver consisting mostly of small and large round cells but with a considerable number of neutrophils. This can be sharply differentiated from the lymphoblastic foci of hyperplasia in Dog 25. The liver cords show extensive focal necrosis, confined more to the central and intermediate parts of the lobule. An attempt at fibrous repair is also in evidence. This condition has evidently developed from an extension of a splenic portal thrombophlebitis or from a general pyemia. The former is more likely, the primary focus being the multiple abscesses in the foreign-body tumor described above. The phago-

cytic activity in this dog is in harmony with the blood picture prior to death where an increased blood destruction with release of cellular débris leads to phagocytic stimulation.

Lymph Nodes. The lymph nodes show a hyperplasia of the endothelial and reticular elements. Eosinophils and plasma cells are very abundant. The follicles fail to stand out prominently. The reticuloendothelial cells appear in the sinuses, particularly in the medulla, as free active macrophages. In some instances the free macrophages in the sinuses are so numerous as to fill these channels completely.

Bone Marrow. There is a marked hyperplasia of all elements of the bone marrow, both of the stroma and the free cells in the meshes of the stroma (increased hematopoiesis). Conspicuous in the stroma is the undifferentiated cellular syncitium and typical phagocytic reticular cells or histiocytes (Fig. 8). Thin walled sinusoids are large and numerous. The littoral cells show considerable phagocytic activity; here and there they are seen rounded off and appearing as large free macrophages floating in the blood sinusoids. Only scattered single fat cells are found.

The various cell types of the hemopoietic tissue are irregularly scattered and mixed throughout the tissue. Most of the hemopoietic elements are young forms: erythroblasts and myelocytes with neutrophil, basophil and eosinophil granules. There are also large non-granular basophil cells of lymphoid nature, regarded as hemocytoblasts. Mature myeloid elements including the non-nucleated erythrocytes and the three types of granular leukocytes as they occur in the circulating blood are found everywhere between the other cells. Megakaryocytes are found scattered evenly among other elements. Some of them are enormous in size.

Lung. The early active infectious period (Dog. 1052) showed little change microscopically. Findings of exudative inflammation were wanting. In the later infective stage reticular elements were quite numerous and often filled with blood pigment. Free and fixed macrophages in the alveoli and interalveolar walls contain a varying number of hemosiderin and dark colored granules ("heart failure" cells).

Kidneys. Many of the glomeruli show necrosis with partial loss and disappearance of the glomerular structures. The endothelial cells of the glomeruli are for the most part swollen and the capillaries collapsed. The endothelium of Bowman's capsule does not show a proliferative action. Occasionally a small collection of serum is seen in the subcapsular space. The tubules show various stages of degeneration even to the point of complete necrosis (Fig. 9). The tubular epithelium where still present has lost its nuclear elements, contains fat droplets and appears flattened. The picture is that of a severe nephrosis with some involvement of the glomeruli. Perla and Gottesman[14] regard the severe nephrosis encountered in Bartonella muris infection as due, not to the severity of the systemic infection, but to the irritation incident upon excretion of large amounts of hemoglobin.

GROUP II. *Post Infection Period. Liver.* The liver shows focal necrosis confined principally to the center of the lobules around the central veins (Fig. 10). In these areas the cytoplasm contains abundant fat droplets. The Kupffer cells are small and normal in appearance, mostly in a resting state showing little phagocytic activity. Yellow brownish bile pigment is seen only in scattered intralobular capillaries. Here and there small collections of lymphocytes are encountered in the periportal areas. These foci are composed of small lymphocytes and seem to arise in the reticular tissue about the periportal areas.

Lymph Nodes. In these nodes the hyperplasia is not as pronounced as in those taken from the dogs autopsied during the acute infectious period.

The general picture, however, bears some resemblance as regards reticular and endothelial proliferation, the latter often blocking the sinuses and no doubt playing the rôle of active macrophages. With the abnormal blood destruction in these cases either partially or completely checked, the diminished cellular débris allows the excess number of active macrophages to revert to the resting or undifferentiated syncitium.

Bone Marrow. Hyperplasia of all the elements of the bone marrow is still observed, perhaps not in degree comparable to that encountered in the dogs of the anemic phase but nevertheless definitely marked. Erythropoiesis and myelopoiesis are prominently in the foreground. Megakaryocytes are present in abundance.

Lungs. In the lungs nothing of a striking nature is revealed. Reticular elements are somewhat numerous and some are seen carrying blood pigment in varying amounts. Localized collections of lymphocytes, conspicuous in the liver, are not so abundant in the lungs. They are seen in small numbers scattered about the bronchi. There is no evidence of inflammation. The peribronchial lymphocytic elements are not an expression of inflammation, but of lymphoblastic hyperplasia of the peribronchial lymphoid follicles.

Kidney. Several areas of lymphoblastic hyperplasia with reticular activity in the background are prominently displayed in kidney sections from Dog 312. The kidney structures otherwise present nothing abnormal. Replacement fibrosis of old tubular destruction occurs as the outstanding feature in Dog 24. The changes are confined chiefly to the collecting portion of tubules.

Dog 269 (control). The microscopic examination confined itself as in the other dogs to the liver, lymph nodes, bone marrow, lungs and kidney.

Liver. There is an apparent increase of Kupffer cells, which are mostly filled with trypan blue as are also the reticular cells found in increased numbers in the periportal areas. This hyperplasia dates back, no doubt, to the time of administration of trypan blue 10 months prior to splenectomy.

Lungs. In the lung there is a considerable accumulation of pigment peribronchially, but no further microscopic changes of note occur.

Lymph Nodes. Pigment deposit with replacement fibrosis is conspicuous throughout the section. Actual hyperplasia of reticular elements to a striking degree cannot be said to exist.

Bone Marrow. A moderate degree of hyperplasia was observed in the various elements of the bone marrow. It might be mentioned, however, that the actual amount of red type marrow found at autopsy in the usual sites of distribution was small.

Kidney. In the kidney section only one small area occurred where definite lymphoblastic and reticular activity was manifested. In scattered areas the tubules within a fibrous zone are atrophied and show various degenerative epithelial changes.

It must be admitted that from the evidence derived from the examination of one control dog, definite and adequate conclusions are impossible. The observations of Weicksel and Gebhardt[11] on a series of dogs, splenectomized, some a shorter—some a longer time (weeks, months, years) revealed nothing in the reticuloendothelial organs which appeared strikingly pathologic. The only finding that did not perhaps seem entirely normal to them was a moderate increase of Kupffer cells in the individual animals. They conclude, "that in dogs in which extirpation of the spleen dates back to more

than a month the increase of Kupffer cells in the liver is at least possible."

On the other hand, the accumulated experimental data of Pearce *et al.*[16] in reference to changes in the bone marrow, liver and lymph nodes of numerous splenectomized dogs, show that during the early periods, 1 to 3 months, the change in the marrow is slight. After the lapse of 6 months, however, the fat tends to be completely replaced by marrow cells. In the lymph nodes they found an increase of endothelial cells in a large proportion of dogs that had been splenectomized for periods of 2 weeks or more. The phagocytic Kupffer cells of the liver were in most instances also increased. The bone marrow hyperplasia they regard not as compensatory to the anemia caused by splenectomy, but rather as an expression of bone marrow actively in taking over the hemolytopoietic function of the spleen in its absence. The findings in the liver and lymph nodes also suggest the development of a compensatory phagocytic function for the loss of the spleen.

Discussion. Thus one finds that both the early and the late infectious periods are marked by changes confined almost exclusively to the reticuloendothelial elements of various organs. In the post-infection period these changes are still observed but here the picture is one of less activity and a reversion of the active differentiated phagocytic cells to the resting or undifferentiated elements. Furthermore, in examining blood smears one is struck by the excessive amount of cellular débris in the form of broken down erythrocytes present in the circulation. This blood destruction is dependent upon Bartonella organisms finding abode in the red cells. With the rapid blood destruction that follows their entrance and with the subsequent cellular débris accumulating in the circulatory blood, a mechanism for the removal of this débris is called into play, hence the enormous activity of the phagocytic endothelial and reticular cells throughout their principal sites of distribution.

The liver, lymph nodes and bone marrow being perhaps after the spleen richest in reticuloendothelial elements, it follows that phagocytic activity should be conspicuously demonstrated in these organs. In the liver this activity is manifested by the proliferation of the Kupffer cells. According to Maximow,[13] "the tortuous sinusoids of the liver are interposed between the portal and the hepatic veins so that the blood pressure is exceptionally low and the blood stream very low. Such an arrangement facilitates the removal of substances from the slowly passing blood and enables the Kupffer cells maximum opportunity to take up foreign particles."

The focal necrosis seen so conspicuously in the liver and to some extent in the kidneys and other organs may in all probability be explained by capillary thrombosis, leading to an ischemic de-

generation of dependent regional areas. Perla and Gottesman,[14] in studying the pathologic lesions of Bartonella muris in the lymph nodes, regard them as the result of hyperactivity and subsequent exhaustion of the endothelial elements. These same authors regard the two outstanding types of lesions in the kidneys, viz., focal necrosis and tubular degeneration as resultant upon endothelial destruction by the infectious process and excretion of hemoglobin and other irritating toxic substances of blood-cell destruction.

The marked hemopoietic activity in the bone marrow is the usual picture of regeneration seen in other severe grades of anemia. The severe anemia often developing in a short time leads to a state of anoxemia of the tissues with various progressive parenchymatous degenerative lesions, especially in such cellular organs as the liver and kidneys. The icteric tinting of tissues and hemoglobinuria encountered at the height of the Bartonella infection is but another manifestation of marked blood destruction and possible liver injury.

The persistent changes observed in the dogs free from an active infection for months and after they had recovered from a severe anemia may in all probability be looked upon as compensatory for the loss of the spleen. These changes are associated, no doubt, with immunity to further infection with Bartonella canis. Dog 24 could not on repeated attempts be reinfected 2 months after the last appearance of organisms in blood smears. Dog 269 (control), splenectomized 160 days prior to autopsy and free from organisms throughout this time, failed to show typical histologic compensatory changes. Perla[15] is of the opinion "that a compensatory mechanism to splenectomy develops only as a result of a physiologic need and in the absence of the Bartonella virus such a physiologic compensation for the protective action of the spleen does not develop." The compensatory changes are seen in the lymph nodes in the form of reticuloendothelial hyperplasia, in the bone marrow in the form of hyperplasia of all the tissue elements and in the liver and lung in the form of lymphoblastic collections periportally.

Summary. The course of Bartonella canis infection transmitted to 5 otherwise normal splenectomized dogs has been presented. The incubation period after injection with Bartonella in the different dogs varied from 7 to 15 days. During the infection cycle the organisms appeared and disappeared periodically from the blood stream. No definite regularity as regards sequence and duration of periodic attacks and intervals of freedom from organisms was observed in the individual dogs or in the animals as a group. Associated with the Bartonella infection was a progressive cyclical secondary anemia, leading to general emaciation and physical weakness. The animals recovered and the blood approached normal

levels as soon as the severity of the infection began to wane. No fatality occurred in our dogs.

The gross and histologic necropsy findings, of the chief reticuloendothelial organs in dogs during the active infection stage and after the infection had run its course are presented. Most striking is the marked phagocytosis in the active stage and changes compensating for the absent spleen in the later stage. A control dog is also included and reference is made to the histologic changes observed in simple splenectomized dogs by various workers.

A brief consideration of the activity of the reticuloendothelial elements occurring in Bartonella infection throughout their principal sites of organ distribution is given.

I acknowledge indebtedness to Dr. Edward B. Krumbhaar for suggesting and guiding the investigation, and to Dr. Eugene A. Case for assistance in the pathological interpretations.

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THE PRESENCE OF THE INTRINSIC FACTOR OF CASTLE IN THE GASTRIC JUICE OF PATIENTS WITH PERNICIOUS ANEMIA.*

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Since Fenwick, in 1877, and Cahn and von Mehring, in 1886, called attention to the relationship of gastric secretion and pernicious anemia, there has been considerable speculation concerning the etiology of this disease. Recently, Castle, Townsend and Heath[1] postulated that an "intrinsic" factor was necessary for the development of a substance which caused red blood cells to mature, and that this substance was present in gastric juice obtained from apparently normal individuals, but absent in the gastric juice of patients with pernicious anemia. While this hypothesis is of the greatest importance, it does not explain adequately (1) the characteristic spontaneous remissions which occur in pernicious anemia; (2) why patients in relapse have variable red blood cell counts; and (3) why those patients with pernicious anemia who apparently have no "intrinsic" factor in their gastric juice are able to produce at least some mature red blood cells, despite the specific conclusion that the intrinsic factor must be present in order to accomplish this.

In an attempt to explain some of these questions, the following experiments were performed with gastric juice obtained from patients with pernicious anemia in relapse. The patients selected were proven to have pernicious anemia by their history, physical findings and laboratory procedures. The red blood cell counts were made on a Neubauer-Levy counting chamber (new ruling, U. S. Bureau of Standards). The hemoglobin was calculated in a Sahli hemoglobinometer according to the recently modified method of Osgood and Haskins. The reticulocyte counts were made on brilliant cresyl blue stained cover-slip preparations, and on each occasion 1000 red blood cells were counted.

Since the gastric secretion in pernicious anemia is markedly reduced in amount,[2,3] continuous aspiration of the stomach for 3-hour periods by means of a water suction pump (10 cm. mercury pressure) was necessary to obtain sufficient quantities of juice. The specimens were obtained under fasting conditions without histamin stimulation, as it was noted that this substance did not alter the gastric secretions in pernicious anemia. When the specimens were collected, sufficient concentrated hydrochloric acid was added to

* Presented at the meeting of the American Society of Clinical Investigation, Atlantic City, N. J., May, 1935.

produce a hydrogen-ion concentration of pH 2, and the material was then stored in the icebox for variable periods of time. Gastric juice samples were obtained at intervals from 26 patients in relapse, and a total of 177 observations were made on the volume of gastric juice secreted per hour.

The average gastric-juice volume in the normal individual is approximately 150 cc. per hour.[3] In patients with pernicious anemia, the average gastric-juice volume was found to be approximately

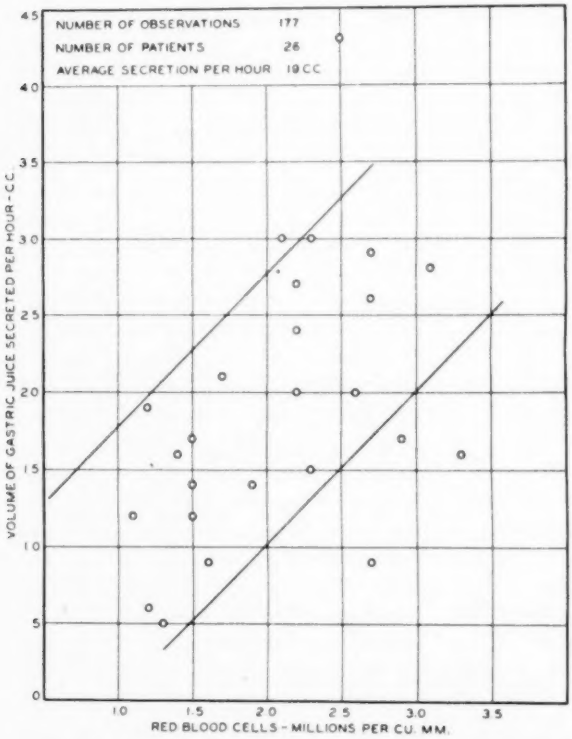

CHART I.—The relation between the average amount of gastric secretion and the red blood cell level in pernicious anemia (relapse).

20 cc. per hour, although there was considerable variation in individual patients. The extremes of gastric secretion were 4 and 45 cc. per hour. From the figures plotted in Chart I, it appears that in untreated pernicious anemia patients in relapse there exists a direct relationship between the amount of gastric juice secreted and the level of the peripheral red blood cell count. Consequently, it may be inferred that the blood stimulating factor of the gastric juice varies with the volume, and that with decreased gastric secre-

tion there is a corresponding decline in the red blood cell count. From these observations, it is suggestive that the so-called intrinsic factor in pernicious anemia is deficient in quantity rather than quality,[9] and the rate of hematopoiesis is dependent upon the quantity of intrinsic factor produced.[8]

In suggesting the previous conclusion, it has been assumed that the gastric juice obtained from patients with pernicious anemia contains the active principle or the so-called intrinsic factor. The following three experiments justify this conclusion.

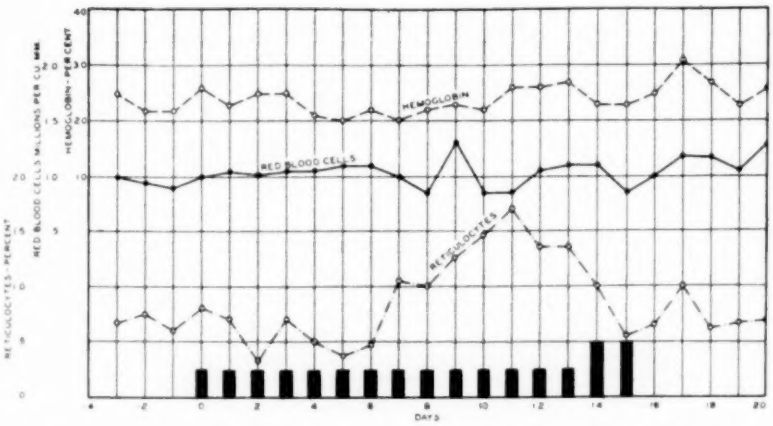

CHART II.—The effect on a case of pernicious anemia of the daily administration of pernicious anemia gastric juice incubated with beef steak.

Experiment 1. The gastric juice used in this experiment was obtained from 5 untreated patients with pernicious anemia in relapse (red blood cell counts varying from 1.5 to 3.3 millions per cmm.). It was collected during a period of 8 weeks and stored in a refrigerator until 1500 cc. had been obtained. A daily dose of 150 cc. of gastric juice was incubated with 200 gm. of meat for 2 hours, at pH 2 and later made pH 5. This was fed for 10 consecutive days to a patient with typical pernicious anemia, whose initial red blood cell count was 1.93 million per cmm. and hemoglobin 51% (Sahli) 7.14 gm.%. Table 1 shows that a rise in the percentage of reticulocytes started on the 10th day and reached a maximum of 9.8% on the 13th day. This was accompanied by an increase in the number of red blood cells and in the hemoglobin percentage. From the 10th to the 19th day no further treatment was given and the reticulocyte percentage fell to the pre-treatment level. This response[9] is similar to those which were previously reported as indicative of the presence of the intrinsic factor in normal gastric juice.[4]

Experiment 2. The preceding experiment was repeated in order to rule out the possibility of a spontaneous remission. The procedure varied slightly in that the gastric juice feedings were given over a longer period of time. For a period of 12 weeks gastric juice was collected from 10 patients with pernicious anemia in relapse. A total of 2545 cc. was obtained. For 13 consecutive days, the subject (pernicious anemia in relapse) ingested

150 cc. of gastric juice incubated with beefsteak, and for the last 2 days the dosage of gastric juice was doubled. Chart II shows that a rise in the reticulocyte percentage started on the 7th day and reached a maximum of 16.2% on the 11th day. A secondary rise of the percentage of the reticulocytes occurred on the 3d day after the dosage of gastric juice was doubled.

TABLE 1.—THE EFFECT ON A CASE OF PERNICIOUS ANEMIA OF THE DAILY ADMINISTRATION OF PERNICIOUS ANEMIA GASTRIC JUICE INCUBATED WITH BEEFSTEAK.

Date (1934)	R. B. C. (million per cmm.)	W. B. C. (per cmm.)	Hemoglobin (%)	Reticulocytes (%)	Day of treatment	Type of treatment
1/ 9	2.3	5600	57	...	–3	
1/10	1.93	4200	51	2.7	–2	
1/11	....	....	..	5.2	–1	
1/12	....	....	..	1.8	0	150 cc. of gastric juice plus 200 gm. beefsteak.
1/13	....	....	..	5.7	1	" " "
1/14	....	....	..	5.2	2	" " "
1/15	....	....	..	4.6	3	" " "
1/16	....	....	..	3.5	4	" " "
1/17	....	....	..	4.9	5	" " "
1/18	....	....	..	3.5	6	" " "
1/19	1.85	5000	49	5.3	7	" " "
1/20	....	....	..	5.2	8	" " "
1/21	....	....	..	3.8	9	" " "
1/22	....	....	..	6.5	10	
1/23	1.76	4800	52	8.1	11	
1/24	....	....	..	9.4	12	
1/25	....	....	..	9.8	13	
1/26	2.29	6100	60	6.3	14	
1/27	....	....	..	6.5	15	
1/28	2.31	....	60	6.8	16	
1/29	....	....	..	7.3	17	
1/30	1.95	....	56	5.0	18	
1/31	....	....	..	4.2	19	
2/ 1	2.19	6950	61	5.7	20	

The results obtained in these 2 experiments are most suggestive of the fact that pernicious anemia gastric juice contains the active principle, and the presence of this substance accounts for the limited hematopoietic activity which did occur in the two experiments just described.

Experiment 3. If the intrinsic factor in reduced amounts is present in the gastric juice of patients with pernicious anemia, it was thought that additional information bearing on this question might be obtained by the following procedure: obtain a relatively large amount of gastric juice from a patient with pernicious anemia in relapse and then administer it to the same patient for a short interval in concentrated form. Daily specimens were obtained by aspiration of the gastric secretions for a period of 20 days. A total of 760 cc. were collected. Because of the small amount it did not seem practical to administer it orally; and since previous investigators[5,6] had proven the effectiveness of intramuscular injections of normal gastric juice, this method was chosen. The gastric juice was concentrated

under reduced pressure to 12 cc. This amount was divided into two equal doses and given on successive days. At the onset of treatment, the red blood cell count was 2.6 millions per cmm. and the hemoglobin 76%. Chart III shows an initial increase of the reticulocytes on the second day, a maximum peak of 7.4% on the 10th day and then a return to the pre-treatment level. Since there are no standards by which to compare this response, it can only be concluded that pernicious anemia gastric juice contains the intrinsic factor. If one wishes to compare the results with the reticulocyte standard of oral administration of liver extract or desiccated stomach,[7] the peak in this experiment reached the calculated response for this individual.

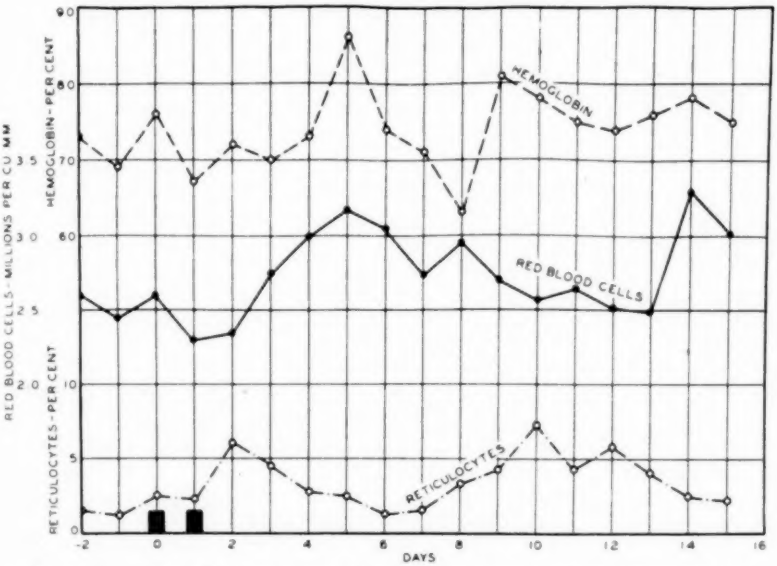

CHART III.—The effect on a case of pernicious anemia of two intramuscular injections of the patient's gastric juice (concentrated).

From the experiments described, it appears possible to explain why patients with pernicious anemia are able to maintain a limited amount of hematopoietic activity, and why different patients have different rates of red cell formation. Apparently erythropoiesis depends in part, at least, upon the action of the intrinsic factor, and the rate of red blood cell formation is related to the amount of the intrinsic factor produced. Spontaneous remissions still remain in the realm of speculation.

Conclusions. 1. The intrinsic factor of Castle is present in the gastric juice of patients with pernicious anemia in relapse.

2. The deficiency of the gastric secretion in pernicious anemia appears to be quantitative rather than qualitative.

3. The red blood cell count, in relapse, falls to a level determined by the amount of intrinsic factor which the patient is able to secrete in his gastric juice.

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THE TREATMENT OF CORONARY ARTERY DISEASE BY INTRAVENOUS INJECTIONS OF HYPERTONIC SALINE SOLUTION.

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The favorable results achieved by Silbert[1] in the treatment of patients suffering from thromboangiitis obliterans, by repeated intravenous injections of hypertonic saline solution, suggested the possibility of applying the same principle of therapy to arterial disease of the heart. Silbert administers hypertonic salt solution in 300 cc. doses intravenously, 3 times weekly. Patients so treated soon lost their pain. Although the disease process differs essentially in coronary sclerosis, the therapeutic objective, the development of collateral circulation, is identical in the two conditions.

The author harbored this belief for 6 years, but feared to give intravenous saline injections to patients with coronary artery disease. Three years ago, however, an opportunity occurred to observe the effect of this therapy. A patient having arteriosclerotic closure of the leg vessels and coronary disease, was given intravenous therapy accidentally before a cardiac examination was made. Three

injections of 5% sodium chlorid solution of 300 cc. each had been given to the patient before the diagnosis was known. A cardiac study then revealed that he had had a coronary thrombosis 10 years previously. Since that time he had been unable to walk more than 5 to 6 city blocks. Beyond this distance he was stopped by precordial pain. His electrocardiogram taken on February 15, 1932, showed a diphasic *T* wave in Leads I and II (Fig. 1). Because his precordial pain on walking completely disappeared on the first 3 injections, the intravenous injections were continued. During the following 3 years of this treatment he had only one episode of angina. This occurred after the patient had an altercation with members of his family. The attack lasted only 1 day. At the present time he receives a weekly injection of 300 cc. of a 5% solution of sodium chlorid. Today he can walk any distance without symptoms.

During this 3-year period 15 other patients with combined arteriosclerotic closure of leg vessels and coronary artery disease have been treated with intravenous injections of hypertonic salt solution. No untoward accident has occurred. The results in these 15 cases appeared so promising that 6 intractable cases of angina pectoris due to coronary artery disease without arterial involvement of the extremities were selected for special study. The group consisted of 5 cases of angina pectoris following coronary artery thrombosis and 1 case of coronary sclerosis in a diabetic. These patients had had coronary artery disease for at least 6 months and had not improved under the ordinary course of treatment, which consisted of a restricted diet, cessation of smoking, drugs when indicated, physiotherapy and prolonged rest. None of the 6 patients could walk one block without being stopped by precordial pain or dyspnea.

THERAPY: The initial dose was 100 cc. of a sterile 5% sodium chlorid solution. Subsequent doses were increased by 50 cc. weekly up to a maximum of 250 cc. Injections were given 3 times weekly. If precordial pain occurred during, or immediately following, the increased intravenous injection, it was evident that the heart was not ready for it. The author continued the therapy with the previous dose for a period of 3 weeks. The increased dose was then retried and was in every case successful. A graduated 300 cc. burette was used and the solution was given intravenously by gravity. The burette was about 3½ feet above the patient who was lying horizontally. Patients were not hospitalized and came to the clinic unattended. Minor untoward reactions occurred in the treatment which will be noted in the clinical description of each patient. These patients did not receive any drugs or other treatment after the intravenous injections were begun.

Case Reports. CASE 1.—P. A. (Hosp. Chart No. 361748), white, male, Puerto Rican, cigarmaker, aged 46, had been on the wards of this hospital twice. The date of his last discharge was February 10, 1934. He was admitted to the hospital for the second time because of severe precordial pain and dyspnea on exertion. A Roentgen ray examination of the left shoulder showed calcific deposits in the region of the left subdeltoid bursa. The discharge diagnosis was coronary thrombosis, coronary sclerosis and chronic left subdeltoid bursitis. For 6 months following his discharge from the hospital he was practically confined to his home because he was unable to walk one block without dyspnea on exertion. He came to the dispensary with the greatest difficulty, not only for treatment of his heart, but also for the pain in the left upper extremity. Neither the heart nor the left upper extremity improved by the ordinary methods of therapy for 6 months.

Physical examination before initiating the intravenous therapy showed: *Heart:* left border in the fifth interspace 8 cm. from the midsternal line. Sounds are of poor quality, regular, 80; no murmurs. Blood pressure 110/80. *Lungs:* clear. No evidence of decompensation. He was unable to move his left upper extremity due to subdeltoid bursitis.

Intravenous therapy was begun on August 17, 1934, with 100 cc. of 5% sodium chlorid solution. The plan outlined above was followed. After the 5th injection the patient was able to raise the left hand a short distance from his side. The improvement continued slowly so that after the 15th injection, he was able to raise the left upper extremity above his head without pain. There has been no recurrence of this pain up to date. The spasm of the left upper extremity was a manifestation of coronary artery disease.

He noticed that he was able to walk two blocks without dyspnea after the 6th injection. Here again improvement has progressed steadily. At the present time he can walk from 10 to 15 city block without symptoms. A point of interest was the precordial pain which occurred when the dose was raised to 250 cc. This pain lasted an hour. Taking this as a danger signal, the dose was returned to 200 cc. for 2 weeks. Then when the 250 cc. dosage was again tried, no precordial pain ensued. At present he gets 250 cc. twice a week. His electrocardiogram gave evidence of myocardial damage (Fig. 2).

CASE 2.—A. G. (Hosp. Chart 359000), Russian Hebrew operator, white, male, aged 48, had been in the wards of this hospital on 3 occasions. He was discharged on November 18, 1933, with the diagnosis of coronary artery thrombosis and coronary sclerosis. On his last hospital visit a venesection was done because of heart failure. For 9 months following the last discharge from the hospital, his time was largely spent in convalescent homes. He was unable to walk up a flight of stairs because of angina pectoris and dyspnea and could only walk one block on level ground.

Physical examination of the chest before saline treatment was started, was: *Heart:* the left border was in the fifth interspace 9 cm. from the midsternal line. Sounds were regular, fair, 92; soft apical systolic murmur. Blood pressure was 140/100. *Lungs:* clear. No evidence of decompensation. His electrocardiogram is shown in Fig. 3.

Intravenous therapy was begun on August 17, 1934, with 100 cc. of 5% sodium chlorid solution. The same procedure was followed as outlined. On the 7th injection, he found he could walk two blocks without distress. He experienced no cardiac complaint under a steadily increasing dosage. After a month's treatment he was able to walk 4 blocks without distress. After 9 months' treatment his range of activity is from 4 to 8 city blocks.

CASE 3.—A. B. (Hosp. Chart No. 363119), Russian Hebrew tailor, white, male, aged 63, has been in and out of the hospital wards many times during the past 12 years. When his attacks of precordial pain with radiation down

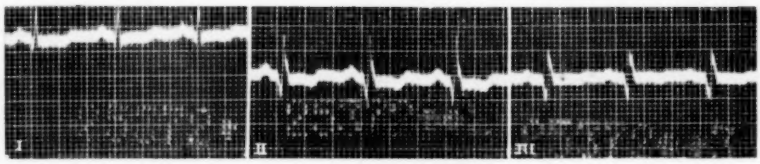

FIGURE 1

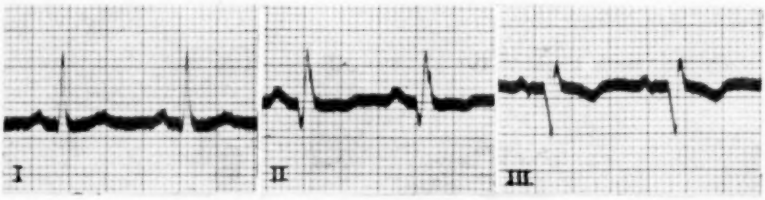

FIGURE 2

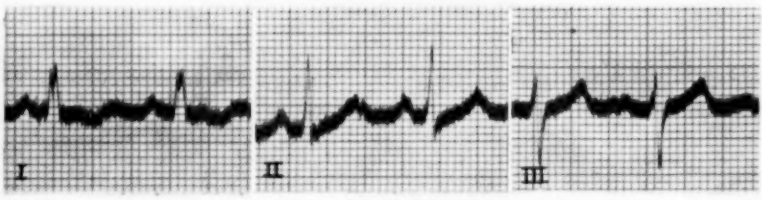

FIGURE 3

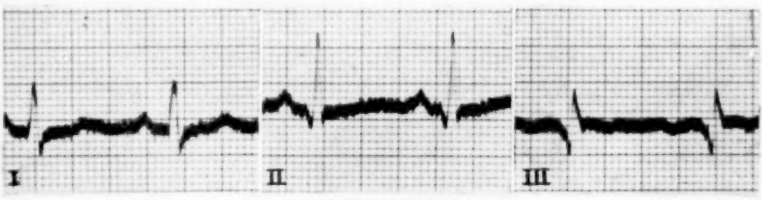

FIGURE 4

FIG. 1.—*T* waves in Leads I, II and III diphasic. *Q* waves in Leads II and III deep.
FIG. 2.—*T* wave in Lead I low, diphasic in Lead II, and inverted in Lead III. *Q* wave in Leads II and III large.
FIG. 3.—*T* wave in Lead I diphasic. *Q*–*R*–*S* notched and slurred in all leads.
FIG. 4.—*T* wave in Lead II low and diphasic in Lead III. *Q* wave in Lead III deep.

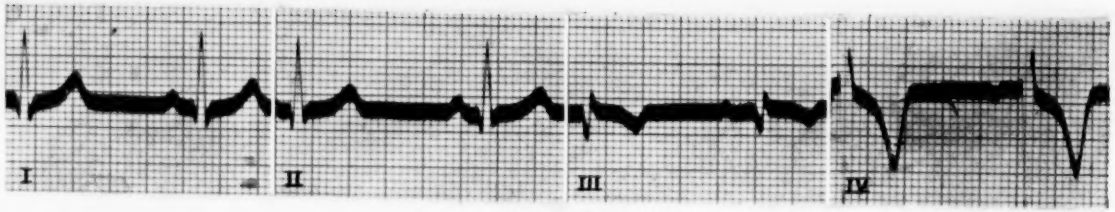

FIGURE 5

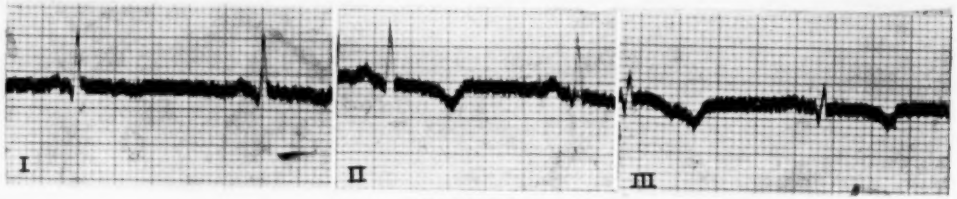

FIGURE 6

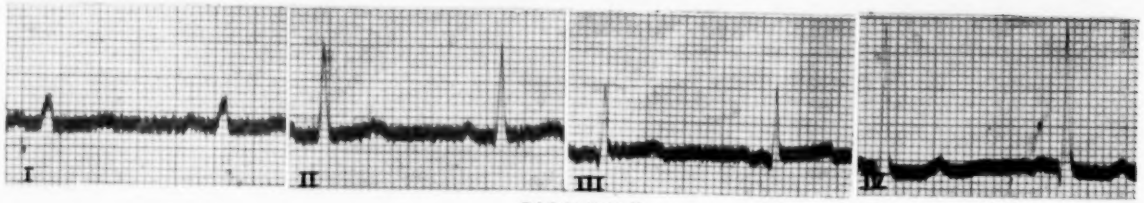

FIGURE 7

Fig. 5.—*T* wave in Lead III inverted. *Q* wave in Lead III deep. *T* wave in Lead IV very prominent. This electrocardiogram is not conclusive. The diagnosis of coronary artery thrombosis and sclerosis was made on the clinical course of the case.
Fig. 6.—*T* wave in Lead I flat, inverted and cove plane in Lead II, and inverted in Lead III.
Fig. 7.—*T* waves of low voltage in all leads, and upright in Lead IV.

his left arm became too severe, hospital care resulted in the amelioration of symptoms. Two and a half years ago, it was noted that he had sugar in his urine and since then he has been under a special dietary regimen. During the past 6 months he has been unable to walk a block without having excruciating, clamping precordial pain. He was compelled to take to bed during this period at least 3 times a week. Nitroglycerin was the only drug which relieved him.

Intravenous therapy was started on August 17, 1934. This patient first noticed improvement about 2 weeks after the therapy was begun. In the course of treatment he was able to walk to the hospital which was 5 blocks away from his home without experiencing pain or other symptoms. The treatment was stopped for a period of 5 weeks because jaundice developed. But after this cleared up, treatment was resumed. At present he gets 200 cc. of the solution twice a week and is able to walk 6 city blocks without pain.

His electrocardiograms never showed any abnormality until recently; on March 14, 1935, it showed a definite change (Fig. 4).

Case 4.—J. E. (Hosp. Chart No. 373916), Russian Hebrew, operator, white, male, aged 40, was discharged from the wards of this hospital on April 15, 1934, with the diagnosis of coronary thrombosis and coronary sclerosis. Up to the time of instituting saline therapy, an interval of 7 months, he was unable to leave his home because he experienced angina pectoris after walking 1 block. The Master step test confirmed the patient's disability; he was unable to complete the 22 mounts required of him according to his height, weight, age, and sex. He stopped after 5 mounts because of precordial pain.

His chest findings before treatment was begun were: *Heart:* the left border of the heart was in the fifth interspace 9 cm. from the midsternal line. The sounds were poor, regular, 76; no murmurs. Blood pressure was 130/80. *Lungs* are clear. There was no evidence of decompensation. Electrocardiogram (Fig. 5).

Intravenous therapy was begun on November 17, 1934, with a 100 cc. dose. An obstacle in the ambulatory treatment was the great distance the patient had to travel to the hospital. He came to the dispensary from his home completely exhausted and suffered extreme angina pectoris. In order to build up his cardiac reserve he was admitted to the wards of the hospital and remained there 2 weeks. On the wards he received a daily intravenous injection of 100 cc. The Master step test demonstrated his improvement, for he was able to complete the 22 mounts without distress. Ambulatory treatment was again resumed but during the following 3 months he was taken to the dispensary by automobile. However, he returned home on foot. Under treatment his improvement progressed steadily. He can now climb the subway stairs slowly with no difficulty. At present he can walk from 10 to 15 blocks without symptoms.

Case 5.—O. S. (Hosp. Chart No. 371843), Russian Hebrew, white, male, aged 55, was admitted to the wards of this hospital twice. The final note on his first visit on October 3, 1931, showed that he had arterial hypertension of 3 years' standing and had been admitted after 10 months of increasing attacks of precordial pressure, orthopnea, and dyspnea. His electrocardiogram showed cover-plane *T* waves in Leads II and III. He was readmitted to the wards on October 7, 1934, giving an interval history of being followed in the cardiac clinic since his first hospitalization. He felt somewhat better at times during the 3 years, but for the past 6 months he was repeatedly seized with excruciating precordial pain radiating to the back. These attacks were relieved by nitroglycerin tablets. During the attacks he was obliged to sit up in bed and gasp for breath. The date of discharge after his second hospital visit was October 20, 1934.

Intravenous therapy was begun on December 15, 1934, with the initial dose of 100 cc. After 2 weeks of treatment he found he was able to make the journey from his home to the dispensary, 5 blocks away, despite the fact that he had slight precordial oppression. His improvement has progressed slowly. He now receives 2 injections a week. He experienced no chest symptoms on increasing the amount of hypertonic salt solution. Since the fourth dose, about 5 months ago, he has had only 2 severe attacks of precordial pain. He can walk 5 to 10 blocks at present.

His electrocardiogram is shown in Fig. 6.

CASE 6.—F. R. (Disp. Chart No. 33-9226), Russian laborer, white, male, aged 55, was admitted to the dispensary on June 7, 1933, giving a 2 years' history of precordial pain with radiation down the left arm. An electrocardiogram at this time showed a cove-plane *T* wave in Lead I and a slightly inverted *T* wave in Lead II. He was treated at the cardiac clinic in routine fashion for 1½ years but was unable to walk 1 block without severe precordial pain. He took 7 to 8 nitroglycerin tablets a day to relieve the attacks.

Physical examination of his chest before intravenous injection showed: *Heart:* left border in the fifth interspace 9 cm. from the midsternal line. Sounds are poor at the base but are better at the apex. Rate 84; no murmurs. Blood pressure 135/90. *Lungs* are clear. Electrocardiogram on November 3, 1934 (Fig. 7).

Intravenous injections were begun on October 13, 1934, with 100 cc. of the solution. He first noticed that he could walk 2 blocks without angina after the 5th injection. The increasing dosage produced no chest complaints. His improvement has continued until now, after 6 months' treatment, he can walk from his home, 20 blocks away, to the dispensary.

Discussion. These 6 patients with angina pectoris were selected for treatment with intravenous injections of hypertonic salt solution because they were definite and uncomplicated cases of coronary artery disease whose symptoms had not been relieved by the usual forms of therapy. Striking improvement occurred in all. It might be contended that the good results obtained in these cases were on a psychogenic basis. These patients are usually heart conscious and their cardiac status may be improved temporarily by psychotherapy, but clinical experience proves that the pain soon returns. Harlow Brooks,[2] in a recent talk, stated that in his experience, which is large, autosuggestion in true angina was of no permanent value.

It may also be admitted that spontaneous remission of anginal pain and other symptoms may occur under any form of treatment or even without treatment other than a period of rest. The cases employed for this therapeutic experiment were selected because they had all failed to improve spontaneously over long periods of observation in spite of rest, sedatives, and the customary therapeutic procedures.

No claim is made that the arteriosclerotic process responsible for this disease is arrested. The treatment was employed in an attempt to increase the collateral circulation. By postmortem injections Gross[3] has shown that remarkable degrees of collateral circulation may develop in the heart following occlusion of a coronary vessel. He states that the functional condition of the heart

after a coronary occlusion depends upon the richness of the collateral circulation which subsequently develops. The intravenous administration of large amounts of hypertonic salt solution probably favors the development of collateral circulation through the finer ramifications of the coronary system.

Contraindications. In selecting the first cases, care was taken to avoid those that showed: 1, Nephritis; 2, cardiac decompensation; 3, cardiac arrhythmia (except extrasystoles and sinus arrhythmia); 4, arterial hypertension over 180 mm. of mercury. Only further experience will show whether all four must be regarded as definite contraindications to the treatment.

Summary and Conclusion. 1. Six patients with severe and intractable angina pectoris due to coronary artery disease who were seriously incapacitated and had not improved on rest and customary therapy, were treated with repeated intravenous injections of hypertonic saline solution over long periods of time.

2. Definite and continuous improvement has been noted in their clinical condition.

3. The hypothesis is presented that the clinical improvement may be due to the fact that the treatment encourages a more rapid development of collateral circulation in the heart wall.

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CARDIOMEGALIA GLYCOGENICA CIRCUMSCRIPTA.*

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Hypertrophy of the heart in infants due primarily to massive deposition of glycogen has been recognized only within the past few years, and has been regarded as representing a cardiac type of von Gierke's glycogen storage disease. The few cases heretofore reported have shown diffuse involvement of the myocardium. However, the possibility that there exists general hypertrophy of the heart associated with localized glycogen deposits not of neoplastic origin, must be thought of in view of the case of Carrington and Krumbhaar,[1] discussed below.

* Read before the 27th Annual Meeting of the Undergraduate Medical Society of the University of Pennsylvania, April 25, 1935.

Von Gierke's disease, first described in 1929, is a disease of young children characterized by the abnormal accumulation and storage of glycogen in the parenchymal cells of various organs, together with enlargement of one or more of the affected organs. A tremendously enlarged liver and very large kidneys were found by von Gierke[2] in each of his 2 patients. He concluded that he was dealing with some metabolic disturbance, and likened the disorder to the lipoid deposit diseases of Gaucher and Niemann-Pick.

In 1932, Bischoff[3] and Putschar[4] presented the clinical and necropsy findings respectively in a case in which the most markedly involved organ was the heart. Subsequently, Pompe,[5] also, described a case with glycogenic cardiac hypertrophy, without enlargement of the liver. It soon became apparent that there were at least two essential forms of the disease, the hepatomegalic and the cardiomegalic. Of the latter, 10 cases are now accepted as proved.[6]

In the cardiac type the heart may become very greatly enlarged.[4,5,6,7] The myocardium is described as pale, brownish or reddish-pink with possibly grayish streaking. No definite changes have been found in the pericardium, endocardium, valves, aorta or coronary arteries. The histologic picture is striking, for the entire myocardium presents a mesh or network appearance. The spaces of the mesh are of varying sizes and shapes, and the walls are seen, under high power, to be composed of striated fibers. Antopol, Heilbrunn, and Tuchman[7] state that in tangential section the muscle cells appear in the form of "hollow cylinders surrounded by delicately striated protoplasmic walls." The nuclei are usually located at the periphery of the cells. According to Humphreys and Kato,[6] the length of the muscle fibers is from 2 to 4 times normal. Some perivascular fibrosis and thickening of the endocardium have occasionally been reported. Best's carmine stain reveals that the vacuoles are filled with glycogen granules, some being present also in the interstitial tissue but none in the nuclei. Fat stains are invariably negative.

The storage of glycogen may occur in many other tissues. It is interesting to note that in one instance of skeletal muscle involvement not all the fibers were affected to the same degree. Many normal ones were interspersed between vacuolated, glycogen containing fibers.[6]

Pompe[5] was the first to point out that diffuse rhabdomyomatosis and so-called idiopathic hypertrophy of the heart may be manifestations of the cardiomegalic type of glycogen storage disease. Rhabdomyomas are known to contain abundant glycogen.[8] These tumors, which may occur either as single or multiple nodules in the myocardium, or in a more diffuse form, are sometimes said to have a microscopic appearance resembling that found in von Gierke's disease. Pompe cites several such instances, and has even suggested that rhabdomyomas arise on the basis of a disturbed

FIG. 1.—Photomicrograph of cardiac muscle showing area of vacuolization. Low-power view.

FIG. 2.—Photomicrograph of section from the original block of myocardium after staining with Best's carmine stain. Glycogen is represented by the red staining dots which here appear black. Most of the glycogen has evidently been washed out because of the formalin originally used as the fixing medium. High power view.

metabolism and are not neoplastic.[5] However, the histopathology; as discussed in detail by Wolbach[9] and as reviewed recently by Farber,[8] is quite distinctive and dissimilar.

For the unusual condition of so-called idiopathic hypertrophy of the heart in children no adequate explanation of the cause has been given. But at least 1 such case, that of Sprague, Bland and White[10] has been found to belong to the cardiac type of von Gierke's disease (Humphreys and Kato[6]).

In 1924, Carrington and Krumbhaar[1] described a case of idiopathic hypertrophy of the heart the histology of which suggests glycogen storage disease. The patient, a female child of 10 months, was found clinically to have a large heart and a palpable liver and spleen. Two months later she died of a bronchopneumonia, and the large heart was brought to Dr. Krumbhaar for pathologic examination.

At necropsy the heart was found to be greatly hypertrophied, with some dilatation of the left side, weighing 136 gm. instead of the normal for that age of about 35 gm. The endocardium was slightly thickened, the valves were thin and competent, and both the foramen ovale and the ductus arteriosus were closed. The left coronary artery had an anomalous origin from the pulmonary artery just above the posterior cusp and nourished distinctly less than half the heart. Though grossly no differences were observed in different parts of the myocardium, microscopic examination disclosed areas of large wavy muscle fibers showing what was reported as "vacuolar degeneration." This was most marked in the areas supplied by the anomalous artery (Fig. 1). Elsewhere the fibers were large with large rectangular nuclei. A slight diffuse fibrosis was also present in some places. No glycogen or fat stains were made.

The liver was somewhat enlarged, weighing 384 gm., the normal being about 275 gm., and microscopically revealed a fleecy shreddy appearance of the cells. Moderate inflammatory changes were noted in the kidneys.

In view of the possibility of this being a case of glycogen storage disease because of the degree of vacuolization, it was desirable to review the original tissues in the light of more recent knowledge. Reëxamination of the old slides and of newly cut sections from the heart shows many areas of vacuolization both in the walls of the ventricles and in the papillary muscles. Under high power the muscle cells are seen to be large and distended but empty, with no particular changes in the nuclei. The large empty spaces do not resemble those produced by fatty change when a comparison is made with a fatty heart. Certain areas appear to be similar to less extensively involved areas in sections from the proven case of Antopol, Heilbrunn and Tuchman, and are almost identical with the descriptions and photographs of various other authors. Both fat and glycogen stains were made and found to be negative, but this

was to be expected since the gross specimen had rested in preserving solution over 13 years.

As a final measure new sections were cut from the old paraffin blocks in which the tissues had been imbedded, and stained with Best's carmine stain. In the vacuolated areas there can now be observed numerous small, discrete, red stained granules which are present both in the empty spaces and in the remaining substances of the muscle fibers. There are also small granules scattered in the scattered in the adjacent and apparently non-affected, *i. e.*, non-vacuolated, portions and in the interstitial tissue (Fig. 2). Consequently, we are able to say that there is a definite deposition of glycogen in this heart. Even in these preparations there was ample opportunity for much of the glycogen to be dissolved postmortem. We have, therefore, a heart with many localized areas resembling vacuolization which can be shown by means of the carmine stain to contain glycogen. The histology in these parts is not at all like that of a rhabdomyoma but rather resembles that of glycogen storage disease.

The anomalous coronary artery and the mild renal changes were regarded in the original report[1] as insufficient cause for the tremendous general hypertrophy. The possibilities that present themselves are:

1. This case may represent a localized cardiac type of von Gierke's disease. The etiologic factor might be ascribed to a congenital anomalous failure of, or retardation in, the development of the local glycogenolytic enzymes in late fetal life, the "dysontogenetic hypenzymatosis" of von Gierke,[2] or to a localized failure of ontogenetic myocardial development subsequent to "persistance of the fetal type of glycogen metabolism."[7] As congenital anomalies are often multiple, the presence of the anomalous artery lends color to the congenital anomaly concept. The uninvolved areas may be compared to the uninvolved fibers in skeletal muscle in Humphreys and Kato's case cited above.[6]

2. It may represent a stage of recovery in von Gierke's disease.

3. It may be a consequence of the abnormal blood supply from the anomalous artery, or, 4, Glycogen accumulation may be added to the list of possible causes of idiopathic hypertrophy. The histopathology may then be said merely to simulate that of glycogen storage disease.

In the future such cases with areas of apparent vacuolization should be tested for the presence of glycogen.

The descriptive term *cardiomegalia glycogenica circumscripta* is suggested to differentiate this condition from the more diffuse involvement in a typical case of cardiomegalic glycogen storage disease.

Summary. 1. A case of idiopathic hypertrophy of the heart, reported in 1924 by Carrington and Krumbhaar, is reviewed. His-

tologically the myocardium showed many areas of apparent vacuolization similar to those found in the cardiac type of von Gierke's disease. Moreover, the presence of glycogen can be demonstrated in this specimen.

2. Such localized deposits of glycogen in an otherwise unexplained hypertrophy of the heart may represent a localized form of von Gierke's glycogen storage disease, or a healing stage of that disease, or merely a cause of idiopathic hypertrophy.

3. The descriptive term "cardiomegalia glycogenica circumscripta" is suggested for this condition.

My thanks are due to Dr. Krumbhaar for the opportunity to study this material in his department and for suggestions during the course of the study.

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BOOK REVIEWS AND NOTICES

HUMAN PATHOLOGY. A Textbook. By HOWARD T. KARSNER, M.D., Professor of Pathology, Western Reserve University, Cleveland. With an Introduction by SIMON FLEXNER, M.D. Pp. 1013; 433 illustrations, 18 in color. Fourth edition, revised. Philadelphia: J. B. Lippincott Company, 1935. Price, $10.00.

IN the new edition of this standard textbook the chapter on the general pathology of tumors has been completely rewritten, and the sections on the hematopoietic system, the ductless glands and nervous system have been revised and brought up to date. Three hundred references have been added to the bibliography. It is gratifying to note that the excellence of the work has been fully maintained.

M. McC.

A BIBLIOGRAPHY OF TWO OXFORD PHYSIOLOGISTS, RICHARD LOWER (1631–1691) AND JOHN MAYOW (1643–1679). By JOHN F. FULTON, M.A. (OXON.), Sterling Professor of Physiology in the Yale University School of Medicine. Pp. 62; 7 illustrations. Oxford: University Press, 1935. (No price given.)

A WELCOME successor to the author's bibliography of Robert Boyle, this book describes 42 editions of Lower's 5 major works and 18 editions of Mayow's 3 books. In continuation of the idea of humanized bibliography, Dr. Franklin's Introduction and the author's Preface and Epilogue give a background and sidelights that bring these two Oxford physiologists clearly before us. Mayow, in agreement with Paterson's views, is portrayed as the uncritical popularizer; Lower as the independent and brilliant investigator. The valuable point is also emphasized that "scientific ideas should be considered in relation to the soil from which they grow."

E. K.

AGENTS OF DISEASE AND HOST RESISTANCE. Including the Principles of Immunology, Bacteriology, Mycology, Protozoölogy, Parasitology and Virus Diseases. By FREDERICK P. GAY, in association with 19 others, all of whom, except 4, are past or present members of the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York. Pp. 1581; 212 illustrations, 6 colored plates, 125 tables and 61 diagrams. Springfield, Ill.: Charles C Thomas, 1935. Price, $10.00.

THIS extensive treatise by Professor Gay and his associates deals with the etiology of disease in its broadest sense. As stated in the Preface, attention has been centered on principles rather than practice, that is to say, the book contains almost no detailed information as to the technique of the laboratory sciences with which it deals. Since there are a number of excellent manuals on technique, the omission of details of methods allows the inclusion of subjects not usually brought together in book form. The work consists of 12 parts divided into 65 chapters. In the first 5 parts (pp. 1–454) are discussed the general aspects of the causation, classification and nature of disease; inanimate disease agents and tolerance; the morphology and physiology of living disease agents, particularly bacteria;

infection and epidemiology; and resistance and immunity. The sixth and largest part (pp. 455–1070) deals with pathogenic bacteria and diseases produced by them; the seventh with pathogenic spirochetes and spirochetoses (pp. 1071–1108); the eighth with pathogenic fungi and fungus diseases (pp. 1109–1151). In Part IX (pp. 1152–1274) are a number of chapters on filterable viruses and related pathogenic forms. In Part X (pp. 1283–1435) the animal pathogens are treated; with chapters on the pathogenic protozoa, on helminths, and on arthropods as agents and vectors of disease. The next part (pp. 1436–1466) which in the Reviewer's opinion should either be omitted or expanded) discusses diseases of obscure etiology. In the final part (pp. 1467–1562) are presented practical results in the diagnosis, prevention and cure of infectious diseases.

A good selected bibliography is given at the end of every chapter. Over 200 illustrations, some of them colored, and numerous well-arranged tables and diagrams add to the value of a book which will serve not only as an excellent text for the advanced student of bacteriology and allied sciences, but also as a modern presentation of subjects of great importance to the practitioner of medicine who stands in need of a reference work of this kind.

B. L.

Diseases of the Nose and Throat. For Practitioners and Students. By Charles J. Imperatori, M.D., F.A.C.S., and Herman J. Burman, M.D., Professor and Instructor respectively of Clinical Otolaryngology, NewYork Post-Graduate Medical School, Columbia University. Pp. 723; 480 illustrations, some in colors. Philadelphia: J. B. Lippincott Company, 1935. Price, $7.00.

This work contains a wealth of information briefly presented, which should be of great practical value to the student, practitioner and specialist. Methods of diagnosis and treatment of nose and throat conditions are tabulated. Considerable space is devoted to peroral endoscopy.

K. H.

Russell A. Hibbs. Pioneer in Orthopedic Surgery, 1869–1932. By George M. Goodwin. Pp. 136; illustrated. New York: Columbia University Press, 1935. Price, $2.00.

The story of the work and life of a physician is always interesting. When the physician discussed has been responsible for an improvement in the treatment of the sick, such as surgical joint fusion, his story becomes inspiring.

Both physician and layman will find inspiration in this small biography of Russell Hibbs, the well-known pioneer in orthopedic surgery at Columbia, for he wrought both finely and well.

G. W.

Personal and Community Health. By Clair Elsmere Turner, M.A., Dr.P.H., Professor of Biology and Public Health in the Massachusetts Institute of Technology, etc. Fourth edition. Pp. 680; 130 illustrations, 4 colored plates and 13 tables. St. Louis: The C. V. Mosby Company, 1935. Price, $3.00.

The new edition of this admirable book gives every indication of a thorough revision and much new work in hygiene and allied fields is to be found. Although written as a textbook for students of college grade, it contains much that every doctor of medicine should know and which is not to be found in the curricula of many of our medical schools.

Every educated person should know and understand all that this book contains, both from the point of view of caring for and developing personal health and from that of the good citizen. The chapter on Mental Hygiene is to be especially commended. The book is written in a clear, attractive style and with an excellent balance of commonsense and appreciation of the relative importance of a large body of knowledge. G. R.

M..HANICS OF NORMAL AND PATHOLOGICAL LOCOMOTION IN MAN. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor of Orthopedic Surgery, The State University of Iowa, Iowa City, Iowa. Pp. 424; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $8.00.

THIS text, a revised presentation of the author's lectures, is divided into two parts.

Part I, "General Mechanics of Locomotion," covers the history of mechanics of the locomotor system, the definition and scope of kinesiology and its relationship to allied sciences, the relation of the general laws of mechanics to human motion, the center of gravity and methods of determination, the physical properties of bone, the dynamics, electrophysical analysis and coördination of skeletal muscle action. The last chapter is devoted to a discussion on fatigue and recovery.

Part II deals with "Special Mechanics of Locomotion" as applied to the various joints, the spine, the pelvis, respiration and abdominal cavity. There are three chapters on the human gait covering normal and pathologic mechanics. In the last chapter on the rationalization or work in locomotion is discussed the calculation of external work, energy determination and optimum efficiency.

This book is well illustrated with photographs and drawings and contains a wealth of material on the subject which should be of practical value to the practitioner of medicine, teacher of physical education and scientific investigation. To realize its full value the book should be studied and not merely read. T. O.

THE HUMAN FOOT. Its Evolution, Physiology and Functional Disorders. By DUDLEY J. MORTON, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 244; 100 illustrations. New York: Columbia University Press, 1935. Price, $3.00.

AFTER reviewing his work on the evolution of the foot and man's posture, the author takes up the normal physiology of the foot and evaluates the importance of its various parts. Though far from complete, as the author emphasizes in his Preface, it is probably the best monograph in English dealing with the anatomy, physiology and pathology of the human foot. G. W.

APPARATUS AND TECHNIQUE FOR ROENTGENOGRAPHY OF THE CHEST. By CHARLES WEYL and S. REID WARREN, JR., Moore School of Electrical Engineering, University of Pennsylvania. Pp. 166; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $5.00.

THE authors of this volume state in their preface that in order to obtain optimum results in diagnostic roentgenography of the chest, it is essential to have a scientific working knowledge of the physical principles underlying the theory and practice of roentgenographic technique and practice. They have collected such data and knowledge and have presented it in a condensed and attractive form. It is true, they also state, that most roentgen-

ologists are forced by circumstances to spend so much of their time in the practice of their profession and in keeping abreast of medical development that it is impossible for them to make a thorough study of these principles. Up to the present time, all such information has been confined to isolated technical papers and brief references in textbooks emphasizing primarily the interpretative aspects of roentgenograms. The first chapter deals with a summary of the phenomena associated with the production of chest roentgenograms. The inherent inefficiency of the process and the conflicting requirements imposed upon the choice of technique are discussed. In the second chapter on roentgenographic apparatus, the portion describing in detail the advantages and disadvantages of each type of high voltage generator is especially useful to the roentgenologist. The actual roentgenographic technique, the practical application of the principles previously discussed, fills the third chapter. Methods of measurement and standardization of apparatus and technique are found in the fourth chapter. An appendix is added on elementary electrical theory for those who are not currently familiar with the basic principles involved in roentgenography. This book cannot be recommended too highly, not only because it contains material not previously published in book form which makes it valuable as a text as well as a reference book, but also because the technique is based on actual clinical investigations and experience, the result of investigations carried on for 10 years by the authors in the laboratories of the Moore School of Electrical Engineering, University of Pennsylvania, and in the Roentgen ray clinic of the Henry Phipps Institute by Dr. F. Maurice McPhedran. It is a book that should be included in the working library of every roentgenologist.

R. B.

A Terminology of Operations of the University of Chicago Clinics. By Hilger Perry Jenkins, M.D. Pp. 99. Chicago: University of Chicago Press, 1935. Price, $1.00.

In the foreword the author expresses the difficulty often encountered in looking up operations of a certain type in hospital record rooms. The difficulty lies in the varied nomenclature which individual surgeons use for the same operation. The monograph was designed primarily to develop a terminology which could be used with facility as an operation index in any hospital. All synonymous terms have been grouped together, and the subdivision of a main operative term heading has been carried out in certain instances according to the differences in operative technique. The index is complete and was designed so as to be readily available. The work will prove to be very valuable in every hospital which includes surgical services.

I. R.

International Clinics. Vol. IV. Forty-fifth Series, December, 1935. Edited by Louis Hamman, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 331; illustrated, also 2 colored plates. Philadelphia: J. B. Lippincott Company, 1935.

As usual, this number presents a well-distributed subject material by well-known medical and surgical authors. All parts of this country are represented, with one article from England. The papers on Idiopathic Steatorrhea and Hypocytic Leukemia, each with a colored plate, especially attracted this reader. How much better is the latter name than the absurdity of Aleukemic Leukemia! Good, old-fashioned clinical acumen appears in the opening article on Observation of the Tongue, while therapy is represented by 3 articles, empyema, peripheral arterial disease and bacterial vaccines (but for the last, Oh! how pessimistically!).

E. K.

CELSUS DE MEDICINA. (In Two Volumes.) Volume I. With an English translation by W. G. SPENCER, M.D. (LOND.), F.R.C.S. (ENG.). (The Loeb Classical Library.) Pp. 499. Cambridge: Harvard University Press, 1935. Price, $2.50.

OF the 60 odd Latin and almost 100 Greek works that have thus far achieved inclusion in this collection, only the 4 volumes of Hippocrates and Galen's "Natural Faculties" are medical in nature. Thus this volume is the first Latin work to be included in the series. From W. H. S. Jones' Introduction we learn, among the few items known about Celsus, that he probably lived at Narbonne and that this work was but the second of 6 of a large treatise covering agriculture, military arts, rhetoric, philosophy and jurisprudence. Several reasons are given for believing that Celsus was not a mere compiler but practised medicine himself. In addition to the historical summary in the Proemium and the celebrated cardinal signs of inflammation (p. 273), the reader will find much to convince him that Celsus had not the mediocre mind that Quintilian mentions. Like Jones' Hippocrates in this series, the handiness of the format promotes perusal and the parallel pages of Latin and English invite even the veriest tyro of a Latinist to sharpen his faculties on the clear forcible and flowing style of the Latin text. E. K.

THE RANGE OF HUMAN CAPACITIES. By DAVID WECHSLER, PH.D., Chief Psychologist, Psychiatric Division, Bellevue Hospital, New York City. Pp. 159; 11 figures and 22 tables. Baltimore: The Williams and Wilkins Company, 1935. Price, $2.50.

THE modest dimensions of this book are by no means a measure of its inspiration or of the author's achievements. He attains brevity and clearness by a fine hand in the management of his materials and by the excellence of his writing. The first five chapters are a well-written exposition of the problem of measurement and range of human capacities. Even for those less conversant with the intricacies of statistical method, the author succeeds in making clear the method of approach and the pitfalls of statistical logic. His proposal to establish human values in terms of pure numbers is an advance in making intelligible the study of personality, and this method reveals a rather surprising fact, that human capacity as expressed as ratios between extremes of ability have "strikingly recurrent values which fall roughly with the range of 1.2:1 to 1.5:1; in brief, indicating that human variability is relatively limited. The author's discussion of the limitations of analysis, and particularly of the theory of probability as related to measurement of human abilities, should invite wide reading. The remaining four chapters will interest the less mathematically minded reader because of the novel treatment of exceptions, particularly of deficiency and genius and because of the author's developed contention that, contrary to the current doctrine, human capacity has a tendency to reach its zenith in youth and almost steadily to decline from that point on with the advance of age. P. R.

THE PATIENT AND THE WEATHER. VOLUME I, PART I. THE FOOTPRINTS OF ASCLEPIUS. By WILLIAM F. PETERSEN, M.D., Department of Pathology and Bacteriology, University of Illinois College of Medicine, Chicago. Pp. 127, lithographed; 94 illustrations. Ann Arbor: Edwards Bros., Inc., 1935. Price, $3.75.

IT is proposed that this series shall consist of five or six volumes; their release in reverse order—III, II, and the present one—is rather confusing. The responsibility of other factors is admitted but the weather environ-

ment is regarded as a most important one. Complaint is made that we think too pathologically, that we "teach medicine as a science of death." And here one recalls what has elsewhere been said: "There are no diseases, only diseased persons."

In this portion of the thesis, the outstanding chapters are: Changing Restlessness of the Winds in America; Racial Differentiation; Disease, and consideration is here given to endocrine disturbances, anemias, cardiovascular renal disease, epilepsy, cancer, syphilis and acute infection. This most difficult subject is still in the research phase and the author merits praise for his diligence and intelligence in assembling the data in support of the argument he is advancing. An abundant bibliography is included, but it is a matter for regret that indices are lacking. N. Y.

NEW BOOKS.

Injury and Incapacity. With Special Reference to Industrial Insurance. By H. Ernest Griffiths, M.S. (Lond.), F.R.C.S., Surgeon, Albert Dock and Hertford County Hospitals; Consulting Surgeon, Wimbledon Hospital, etc. Pp. 270. Baltimore: William Wood & Co., 1935. Price, $5.00.

Teoria de Los Neoplasmas. By S. Santamaria. Pp. 163; 13 illustrations. Madrid: J. Pueyo, Imp., 1935. (No price given.)

Anatomy of the Rat. By Eunice Chace Greene, Vol. 27 of the Transactions of the American Philosophical Society, held at Philadelphia, for Promoting Useful Knowledge. Pp. 370; 338 illustrations, partly in color. Philadelphia: The American Philosophical Society, 1935. Price, $5.00.

Cold Spring Harbor Symposia on Quantitative Biology, Vol. III. Pp. 359; illustrated. Cold Spring Harbor, Long Island, N. Y.: The Biological Laboratory, 1935. Price, $3.75.

Bauerndoktor. By Menhofers Franzef. Pp. 184. München: Verlag der Ärztlichen Rundschau, 1936. Price, paper, Rm. 2.81; bound, Rm. 3.60.

Aus meinen Krankenblättern. Von der Arbeit eines Landarztes. By Dr. August Heisler, Sanatorium Luisenruhe und Kinderweide Königsfeld im Schwarzwald. Heft 47 of Sammlung diagnostisch-therapeutischer Abhandlungen für den Praktischen Arzt. Pp. 68. München: Verlag der Ärztlichen Rundschau, 1936. Price, paper, Rm. 1.58; bound, Rm. 2.25.

NEW EDITIONS.

Demonstrations of Physical Signs in Clinical Surgery. By Hamilton Bailey, F.R.C.S. (Eng.), Surgeon, Royal Northern Hospital, London; Surgeon and Urologist, Essex County Council; Consulting Surgeon, Clacton Hospital, etc. Pp. 287; 341 illustrations, many in colors. Fifth edition, revised. Baltimore: William Wood & Co., 1935. Price, $6.50.

The Radiology of Bones and Joints. By James F. Brailsford, M.D. (B'ham.), M.R.C.S. (Eng.), Hunterian Professor, Royal College of Surgeons, England, 1934–1935; Radiological Demonstrator in Living Anatomy, The University of Birmingham, etc. Pp. 571; 340 illustrations. Second edition. Baltimore: William Wood & Co., 1935. Price, $9.00.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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STUDIES ON INFLUENZA.

Pandemic Influenza. Pandemic influenza, the severe, highly contagious form of influenza, may reasonably be expected to return if we may rely upon epidemiological history. This review of progress will be an outline of what has been accomplished towards the solution of the many problems of influenza during the last 4 or 5 years, particularly those concerning its etiology. Laidlaw has roughly estimated that in the last great pandemic of 1918–1919 500 million persons were attacked and 15 million lives were lost. With such a tragic possibility before us it may be well to consider whether the medical profession is prepared to focus its attention on specific problems demanding specific answers or whether it will be again confused in a maelstrom of phenomena with its energies scattered and ineffective. The actual difficulties must be clearly recognized and the limitations of what may be hoped for defined.

Definition of Influenza. There is no agreement among clinicians as to just what is meant by influenza and this constitutes today the greatest difficulty in the scientific search for etiological agents. During the pandemic it was generally accepted that we were dealing with a specific disease *en masse*, although only when statistics are available does the individual physician realize that an epidemic is present, and there follows a strong tendency to be swept along by a single diagnosis. The severity of the respiratory symptoms, the high contagiousness, the frequency of a peculiar and often fatal pneumonia associated with cyanosis, the evidence for lack of bodily defense as seen in the common occurrence of a leukopenia, the muscular and other aches and pains, and the early asthenia so often prolonged into convalescence, all these make up the syndrome called influenza. However, the individual cases are widely different from each other and from the etiological side this

is immensely confusing. Many consider that the mild and practically non-fatal influenza should be differentiated from influenza with pneumonia (Gundel, 1933), and that the cases in a pandemic have not the same etiology as the sporadic or smaller epidemic cases (Selter, 1933). Still others find it difficult to separate individual cases of influenza from the so-called "cold" diseases (Meyer, 1933). Berger *et al.* (1934) regard the smaller epidemics as only quantitatively, not qualitatively, different from the pandemic of 1918, and that it is the same disease entity, the characteristic leukopenia developing as the disease becomes more contagious. Laidlaw believed many sporadic cases of influenza may not be of the same character as those of the pandemic outbreaks and thought it more honest to diagnose these as P.U.O. (Pyrexia Unknown Origin). Even the contagious common cold with fever cannot always be sharply separated from influenza and although an exact diagnosis would seem to be the crux of the problem in etiologic studies, yet it must be recognized that at present this is impossible, and this fact must be considered in interpreting the results of experimental work. If we accept the familiar 3-day fever to be the same disease as epidemic influenza, and this latter the same as the pandemic type of 1890 and 1918, we certainly have a heterogeneous lot of signs and symptoms of different values in diagnoses and probably depending upon a variety of etiologic factors.

Whatever may be the etiologic contagious agent in influenza, there is no doubt that it increases in virulence and rapidity of spread just preceding and during the beginning of an epidemic and then gradually grows less and less active until in interepidemic times it is relatively innocuous. The epidemiologist demands, before an agent can be accepted as of etiologic importance, that the cycle of its existence be explained.

The condition of immunity in the population as a whole is variable and the individual with a reduced immunity to any agent may permit this agent to begin a process of human passage from person to person with, if enough susceptibles are available, a gradual increase in the contagiousness and later in the virulence of the agent. This theoretical consideration is difficult to study, but some evidence of such an occurrence is desirable in any infectious theory of influenza.

The proof that a particular infectious agent is the primary causative factor in such a disease as influenza is particularly difficult to obtain. The following are some of the requirements that such an agent should fulfill: 1, It should be shown to be in a fully virulent state when isolated from the acute disease and be relatively abundant in the lesions but not necessarily in all the involved tissues; 2, there should be evidence that the agent readily spreads from person to person; 3, the lesions induced in man or animals should closely resemble those found in the natural disease and should not be produced by other agents; 4, the agent should exhibit toxic qualities so that the evident toxicity of influenza may be explained; 5, reservoirs or carriers of the agent, not necessarily nor probably in the fully virulent form nor in large amounts, should be discovered to account for its survival during interepidemic times; 6, the agent should induce specific serologic changes in those having or convalescent from the disease, such antibodies should be

absent in the susceptible and present in the resistant, and all grades of the disease should be accounted for by the relative balance between the virulence of the agent and the immunity in the host; 7, if the agent is only part of a synergistic combination the characteristics of each agent individually must be clearly defined as well as the combined effects.

Hemophilus Influenzæ as a Primary or as an Essential Secondary Agent in Epidemic Influenza. There are widely divergent opinions on the relationship of H. influenzæ to the disease influenza. While the evidence for the virus theory has been accumulating, there has been a tendency to disregard the newer studies in favor of Pfeiffer's bacillus. So much has been learned about this bacillus since the pandemic of 1918–1919 that many of the adverse criticisms have not as much weight today as they formerly had. There are still many prominent bacteriologists who support the etiologic significance of H. influenzæ or who realize that the evidence against it must be reconsidered in the light of present-day knowledge. I shall, therefore, briefly outline certain evidence for and against the etiologic significance of the influenza bacillus.

The finding of influenza bacilli in normal persons or in those suffering from diseases other than influenza is perhaps the strongest argument against its importance. However, the evidence is not very great that H. influenzæ is present as the predominant organism or even in large numbers in normal persons. Thompson and Thompson (1935) have never found it abundant in the normal. It is well established, however, that the hemoglobinophilic bacteria do make up part of the so-called "normal" flora of man. Furthermore, other bacteria of accepted specific pathogenicity are known to be found in normal persons or in other diseases.

Virulence of H. Influenzæ. Our knowledge of the virulence of this bacterium has grown very slowly and is still far from being complete. The early work of Hudson (1922), who used intraperitoneal injections in white mice showed that Pfeiffer's bacillus was often pathogenic and readily invaded the blood stream and that the strains isolated during influenza epidemics at military camps were more pathogenic than strains from other sources. Cultures mixed with pneumococcus were definitely more invasive. Three or four passages through white mice did not appreciably increase its virulence. In 1924 he noted that freshly isolated strains of H. influenzæ were increased in virulence when mixed with recently isolated strains of hemolytic streptococci or with stock strains of Type I pneumococcus, and he showed further that the Pfeiffer bacillus if injected first, acted as a sensitizer of the host to hemolytic streptococci but that the reverse did not occur.

More recent work has clearly shown that H. influenzæ is a most variable microörganism and has established certain criteria for differentiating typical and atypical forms which were partly distinguished on morphologic grounds by earlier workers (Pfeiffer and others), the atypical being often named para-influenzæ. This differentiation was uncertain and not generally accepted as of significant value until Pittman (1931), using non-hemolytic strains specifically requiring the X and V factors, divided the cultures into well defined typical and

atypical types. The typical cultures showed coccobacillary morphology and capsules yielding a specific polysaccharid, grew in smooth colonies and were called the smooth or S type. The atypical tended to grow in longer bacillary up to thread forms, had no capsules and grew in relatively rough colonies and were considered as R forms. The colony differentiation required a clear blood medium such as Lævinthal agar. Kun and Fenyvessy (1932) described similar forms also using nonhemolytic strains requiring X and V factors and believed that the Pfeiffer bacillus varied through a series of continuous and reversible changes, the particular form encountered depending on the biologic conditions of the host at the time. They were able to bring about changes into all the different forms by experiments on animals. The morphology did not always completely correspond to the colony type. The typical coccobacillary form was found in early disease and caused death in white rats and mice after intraperitoneal injections. The atypical occurred later in the disease and never caused death in animals. The virulence could be raised by animal passage. Kairies (1932) studied particularly the pathogenicity of H. influenzæ in mice and believed that the injury after intraperitoneal injection was due to toxin and that true pathogenicity was problematic. Mixtures of streptococci and Pfeiffer bacilli were more active in causing death in mice than was either alone. He advocated the use of Lævinthal agar and inoculation of mice for the isolation of H. influenzæ. Dochez, Mills and Kneeland (1932) found in chimpanzees which developed common colds after inoculation with a virus preparation, that the H. influenzæ in their respiratory tract was transformed from the non-specific R form to the specific S form, and that a reversal followed the return to health.

Pittman (1933) produced in a horse a type specific antiserum with Type B bacteria (a form often occurring in meningitis cases) which prevented the blood stream invasion of H. influenzæ after intraperitoneal injection of mice and rabbits but did not affect the toxicity. Prausnitz (1933) suggested that strains of low virulence are raised in virulence by growing in the respiratory tract of sensitive persons. Kühn (1934) stressed the evidence that H. influenzæ is pathogenic in inflammatory and purulent lesions quite independent of influenza. Hoyle (1934)[1] followed the incidence of the typical and atypical strains in 17 persons from September to March with fortnightly cultures unless evidence of infection occurred when more frequent cultures were made. He used mouse inoculation, heated blood agar, blood broth, penicillin agar (with which Fleming and MacLean (1930) had successfully cultured H. influenzæ of varying morphology from all of 36 normal persons), and determined the X and V factor requirements of all strains and their ability to produce indol. The typical or S cultures corresponding to those described above, were isolated by the mouse method almost always, invading the blood in 70% in mixed cultures, but only in 30% when pure. They were practically never found in normal respiratory tracts but coincided very closely or preceded the onset of a coryza. Of the 32 fully virulent strains 26 were from those with acute coryza, influenza or sore throat and 4 with chronic catarrh, the others were apparently from temporary carriers. A number of the acute coryza attacks were associated with an increase in pneumo-

cocci. Capsules could not be demonstrated on their virulent strains of H. influenzæ. The atypical or R cultures were never isolated by the mouse method; even when numerous colonies appeared on the penicillin agar, they were all non-pathogenic for mice, *i. e.*, did not invade the blood stream, although toxic deaths occurred in some and they were the only forms isolated in the disease-free month of September. Isabolinski and Stratanowitsch (1934–35), who were former advocates of a diplo-streptococcic etiology for influenza, had the opportunity of studying 15 very early cases and isolated H. influenzæ from all of these. Cultures inoculated into the nose of rabbits produced a purulent discharge and the serum of these animals after 15 days showed agglutinins, and complement-fixing antibodies in 2 of 3 rabbits, while in 1 rabbit there were lung lesions. Hoyle (1934)[2] was able to raise the virulence of strains of H. influenzæ provided the initial virulence was such that 0.5 cc. killed a mouse on intraperitoneal injection. He did this by intrapleural inoculation in young rabbits and a series of rabbit passages until the virulence was such that 0.05 cc. killed a mouse. The strain could be kept by this technique at full virulence, the morphology was of the coccobacillary type, the colonies were watery and intrapleural inoculation induced in young rabbits a typical bronchopneumonia which he could not produce by similar treatment with pneumococci of high or low virulence, hemolytic streptococci or staphylococci. However, B. coli of suitable virulence gave a similar result. Although Hoyle does not say that the suitable B. coli cultures were indol producers, it is an interesting possibility since indol is a rather toxic substance. In an earlier report Hoyle (1934)[1] said that 18 of 28 cultures of H. influenzæ of the typical form were indol producers and that all the 27 atypical were indol negative. Rosher (1931), in a study of strains of H. influenzæ, all requiring both X and V factors, found that their pathogenicity in the peritoneal cavity of mice was increased if the X and V factors were injected along with the bacilli. Of 45 indol positive strains, 26% killed mice on ordinary injections and 71% did so when reinforced as above. Of 45 indol negative strains none killed by ordinary injection and only 6% when reinforced. Huntington (1935) studied the forms of H. influenzæ in certain diseases of children and proposed that the watery fluorescent form be called M or mucoid, the ordinary form S or smooth and that R be retained for the rough form described by Holster (1931) and Scott (1929). Since the R form is only an extreme dissociant obtained after prolonged cultivation on media and is not encountered on primary isolations or even in early transfers, the reviewer believes it is unwise to do more at present than accept the fact that H. influenzæ is extremely unstable in its morphologic and growth forms but that attempts should be made to correlate the type forms at the time of isolation with the presence or absence of animal pathogenicity and of disease processes in the patients. I can, therefore, only say that Huntington did not find H. influenzæ in the nose of children in the absence of respiratory disease, that S(M) strains were sometimes obtained on mouse culture only and that his evidence does not show a correlation between the occurrence of S(M) forms (apparently usually determined on subculture) and the type and severity of the disease. Hoyle (1934)[2], with the strains of H. influenzæ

of raised and stable virulence referred to above, attempted to infect rabbits and guinea pigs with intratracheal inoculations of 0.5 cc. pleural fluid containing the bacilli, and obtained hemorrhagic edema of the lungs but could not recover the bacilli from the site of the lesions. In a few of the controls inoculated with media, however, lesions were produced, some of which were as severe as in those receiving the bacilli. A massive dose of 3 to 4 cc. gave a confluent pneumonia and the bacilli were recovered from the diseased lung. The author warned against neglecting the traumatic effect of such inoculations and particularly stressed the toxic effect. Toxic bacilli can without doubt cause marked lesions and the bacilli may be destroyed at the site of the reaction.

The presence of H. influenzæ in the upper respiratory tract of animals used for experiments is important. Dochez, Shibley and Mills (1930) found Pfeiffer bacillus in 92% of the throat cultures and 13% of the nasal cultures of normal apes as contrasted with 47% and 0% from normal man. They also reported the occurrence in a chimpanzee of a spontaneous cold apparently contracted from the keeper which was followed by a fatal bronchopneumonia from which hemolytic streptococci, Pfeiffer bacillus and other bacteria were recovered. These findings, together with the later report of 1932, already referred to, showing the transformation of R to S forms during the course of a common cold, suggests the great difficulty in the interpretation of results after experimental injections under such circumstances. Kairies (1934) described a sporadic influenza epizoötic among fitchets with the recovery from them of H. influenzæ. With material from the lungs of one of these animals a ferret (with throat cultures negative for H. influenzæ for a week) was inoculated in nose, throat and eye and developed a disease with conjunctivitis, catarrh and the diphasic temperature changes described for the virus disease by Smith, Andrewes and Laidlaw (1933). H. influenzæ was repeatedly isolated from this animal. A contact ferret previously free from H. influenzæ, gave positive throat cultures after 3 days and became ill in 6 days. Two fitchets which remained alive became bacillus carriers. The animal caretaker was a carrier since 1918 and his 10-year-old son with chronic pharyngeal catarrh yielded cultures of H. influenzæ. A student working with the fitchets also developed influenza apparently from them, but before the bacteriologic study had started. Kairies also produced the disease in ferrets by repeated spraying with the sputum of a carrier and by a single spraying with the sputum of an acute sporadic case of influenza. In 1935, Kairies reported an outbreak of sporadic cases of influenza in ferrets which occurred in the winters of 1933–34 and 1934–35 with symptoms like the virus disease and H. influenzæ was present in all the diseased animals. The spread of the bacilli from symptomless carriers to other ferrets was also shown to occur. He described certain differences between the bacillus of ferrets which he named Bacterium influenzæ putoriorum multiforme, and the human strains of Pfeiffer bacillus based on colony and agglutination studies and the marked pleomorphism of the former, but it would seem that similar differences can be found among strains of human origin. The H. influenzæ of swine will be considered under the discussion of the virus of swine influenza.

In 1934 Shope used ether anesthesia primarily to suppress the sneeze reflex of his ferrets before intranasal inoculation with swine influenza virus and thus produced a disease more severe clinically and more extensive pathologically than had been previously obtained by those not using an anesthetic. As a result of this, light ether anesthesia has become more or less generally used for all nasal instillations of ferrets, white mice and other animals, and this has opened up a new technique widely applicable to the study of infections of the respiratory tract, especially for the experimental production of pneumonia. I will here consider the use of ether in the study of bacterial infections, but should point out that very little has been done to determine the exact mode of action of the ether. Neufeld and Kuhn (1935) applied the method in their experiments with pneumococci in white mice and obtained a disease picture entirely different from any previously obtained by other methods designed to reduce the resistance before intranasal instillation. This disease picture was much closer to human pulmonary inflammation than any previously obtained. They also showed that ether markedly increased the virulent action of other microörganisms as well as the production of pneumonia after intranasal inoculation, but with direct injections into the lung the ether had not so evident an effect. In tests on guinea pigs infected with pneumococcus the ether gave no such result. They showed by the use of India ink instilled into the nose of anesthetized mice and guinea pigs that in the mice the India ink spreads rapidly into the bronchi and appeared to act like a bloodless intratracheal injection, but in the guinea pig this intensive pulmonary infiltration failed and only small black foci appeared at the lung hilus. This is not the only factor, however, since intrapulmonary injections without ether do not give the same picture or results. In a later study Neufeld and Collier (1935) used this technique for producing pneumonia in mice in a study of various therapeutic preparations. Hoyle (1935) tried to repeat the virus work of Andrewes, Laidlaw and Smith (1934), who had confirmed Shope's results with ether, but he did not agree that the lung lesions induced by the virus in mice were specific. He considered them examples of aspiration pneumonia and was able to produce similar lesions, although more severe, by using pathogenic bacteria and ether anesthesia. Among the bacteria thus successfully used was H. influenzæ which, when fully virulent, killed 21 out of 30 mice, but when less virulent did not kill any of 12 inoculated mice. Filtrates from the lungs of such mice did not carry on the disease, so that he did not suggest that a virus can be so obtained.

There is needed, in order to explain many of the results with this new technique, a thorough comparative study of the finer anatomy and physiology of the respiratory tract of mice, ferrets, swine, man and other animals. The differences in the patterns of ciliary movements in man and monkey on the one hand and the mouse, rat and other animals on the other are described by Lucas and Douglas; but it is only suggestive of the problem before us. St. Clair Thomson's (1935) lecture on "The Defences of the Air Passages" is well worth reading in this connection.

Just a word may be added about the serologic evidence in favor of H. influenzæ. The numerous heterogeneous types as indicated by the

results of agglutination tests are no longer significant because of the antigenic variability of H. influenzæ. Gundel (1934) considered the agglutination test unsuitable to indicate the state of immunity in man and advocated the complement-fixation test, great importance being given to having the proper antigen prepared in the same way as that used in pertussis (Gundel and Schülter). Pittman and Goodner (1935) prepared antisera against well studied strains of H. influenzæ in the horse and the rabbit. Both these sera gave good results by agglutination (of the type specific strains) and precipitin reaction (with the type specific polysaccharid). The complement-fixation test gave positive results with the rabbit antiserum but negative results with the horse antiserum when the polysaccharid was used as the antigen. However, if bacilli (either R or S) are used as antigen, then the rabbit serum gave a complement fixation with all strains of Type B tested and the horse serum was positive with all but one strain. Both antisera contained both rough and smooth antibodies; but if the capsule were well developed as in the above negative strain, they believed the rough antigen was covered and the horse serum failing to fix complement with the polysaccharid could not reach the rough antigen, and the result was negative. The fact that one strain had a more stable capsule than the others is of interest in considering its possible effect on virulence.

If another pandemic of influenza should occur, it would be advisable in order to have the necessary facts in favor of or against the Pfeiffer bacillus to determine the following: 1, The presence of H. influenzæ of the non-hemolytic type and requiring both the X and V factors, in various stages in the onset and course of the disease, and if possible preceding the onset. To do so cultures should be obtained particularly from the nose, throat, sputum, and in pneumonia possibly by puncture from the lung. The technique must include a clear blood agar such as Levinthal agar, and the direct injection of mice in order to determine the form of the bacillus at the time of isolation both as to type of colony, morphology of the bacilli and the relative ease of emulsifying in broth or saline; 2, the pathogenicity of strains by intraperitoneal injection of mice with the primary mixed material as well as with pure cultures and with mixtures of H. influenzæ and the other bacteria present. This would include lethal power, invasion of the blood and survival of the bacilli in the peritoneal cavity; 3, indol production by the strains isolated which can be done from fluid media or by the oxalic acid paper technique over a blood agar slant; 4, the complement-fixing antibodies in the patient's serum using suitable strains of H. influenzæ to identify serologic antibodies against both the type specific polysaccharid of the smooth form or the species specific substances of the "capsule" free form. Agglutination tests may also be useful in certain cases and the facts concerning them should be increased; 5, the relationship of these results to the simultaneous demonstration of a virus-like substance in the filtrates of the patient's secretions.

A Filterable Virus in the Etiology of Influenza. Since most recent writers have reviewed the earlier work which suggested that a filterable virus might be a significant agent in influenza, I need not do so. Dochez and his associates studied filtrates from persons either with the common cold or with influenza and used a long series of human volunteers and

a few chimpanzees as experimental animals. Many of the responses to the intranasal inoculation with supposedly influenza virus closely resembled common cold of varying severity. Cultures of these filtrates in embryonic tissue gave similar results, but all these painstaking experiments lacked in decisiveness, perhaps because man is a most unsatisfactory animal to control.

The virus theory was revivified in 1931 with the brilliant series of articles by Shope on the etiology of swine influenza—"brilliant" being the word applied to this work in nearly every discussion on influenza since. The story of swine influenza has become well known. Briefly, it is that a disease appeared in 1918 among the swine in eastern Iowa which had so many points of resemblance to the pandemic of human influenza that Dr. J. S. Koen named it swine influenza. When the disease breaks out all the swine in the herd become infected in the early autumn and early winter epizoötics, but the mortality is only about 1% to 4%. Shope first showed that the disease could be transmitted by intranasal inoculation of materials from the respiratory tract of sick swine to healthy swine at Princeton, far distant from the locality in which seasonal epizoötics have continued to appear, there being no immune swine and no such disease at or about Princeton. He next proved that H. influenzæ, always present in the sick animals, did not by itself induce the disease when freshly isolated and presumably fully virulent cultures were used. He then tested filtrates of the contagious materials and found that bacterial-free filtrates produced a mild disease in swine, which he called the filtrate disease, but which had not many of the important characteristics of the epizoötic disease itself. The typical epizoötic disease, however, regularly followed the combined inoculation of both filtrate and bacilli. In 1932 Shope showed not only that immunity was conferred to swine by the natural disease and by a single intramuscular injection of the virus—the virus having shown no other demonstrable effect by any other route than the respiratory tract—but also that the bacillus itself produced no immunity. Köbe, in 1933, reported finding a similar virus from a disease of suckling pigs on the island of Reims in Germany which was quite different from the swine pest virus, was spread by contact, required the presence of H. influenzæ to produce the full pneumonic disease and, although it only occurred in young pigs, was probably identical with the virus of Shope. In 1934 Shope's important studies on contagion were reported, in which he showed that three types of infection could occur. 1, Full contagiousness in which both virus and bacillus were transferred by pen contact from the sick to the well; 2, partial contagiousness in which only the virus was transferred and resulted in the mild filtrate disease; 3, the establishment of carriers of H. influenzæ by the disappearance of the virus. In these last two types either the transfer of the bacilli or the virus brought back the full contagiousness of the complex. Following the report of Smith, Andrewes and Laidlaw (1933) on a disease in ferrets induced by filtrates from cases of human influenza, Shope, in 1934, anesthetized ferrets with ether before inoculation and was able to produce a more severe pulmonary disease in these animals with the swine virus alone, the bacteria not being an essential component. He thought that the effects of the ether were to favor the establishment of

the virus, to permit the giving of a larger dose because of the inhibition of the sneeze reflex and to make possible a deeper introduction of the virus. Although he believed that the method of the English workers came closer to the natural infection, nevertheless the fact that the disease produced by the use of ether was more definite, constant and easily recognized made it of value in such experiments. In 1935 Shope confirmed the results of Andrewes, Laidlaw and Smith (1934) and Francis (1934) concerning the transfer of the swine virus to white mice from infected ferrets, and was able to infect mice directly without ferret passage with one of two strains of the field virus of swine influenza, while with the other 2 or 3 mouse passages were needed. In the mouse disease he found no evidence that any significant rôle was played by the bacteria, fatal pneumonias being produced by pure virus infections. After mouse passage the virus remained equally infective for either swine or ferrets, that is, it was a stable virus. The mouse is, therefore, a useful animal for studying the pure virus disease. Most of the comparative work on the human and swine influenza viruses indicates that they are closely related if not identical, the swine virus, however, seeming to be both more stable and more virulent.

The new exciting investigation of human influenza virus began with the preliminary report of Smith, Andrewes and Laidlaw in 1933. These workers, stimulated by the work of Shope and the success of Dunkin and Laidlaw (1926) in discovering the virus of dog distemper by ferret inoculation, used this animal for the study of filtrates from the throat washings of human influenza patients. Intranasal inoculation was followed after about 48 hours by a non-fatal inflammatory disease of the respiratory tract with a diphasic type of temperature response. They were able to carry on the disease picture by inoculating preparations of the turbinates of the ill ferrets into the nose of new animals. The active substance was only recovered from the respiratory tract, neither lymph glands, spleen or blood being ever infective and the respiratory was the only route by which the typical response could be obtained. Contact spread of the disease from ill to well ferrets was mentioned as having frequently occurred but no details of this significant observation were given. The ferrets after recovery from the febrile disease were found to be resistant and the virus when mixed with their serums and inoculated into the nose of susceptible animals no longer induced the typical reaction. Normal ferret serum was said to have had no effect but the number of these tested was not given. Human sera were variable but usually neutralized the virus; for example, 10 human sera of persons recovered from influenza at first neutralized, but on retesting 2 of these failed; 3 sera from cases with no history of influenza failed in 2 instances and was able in 1 to neutralize the virus. The materials studied were the nasopharyngeal washings, often but not always filtered, from: 8 cases diagnosed as influenza, the reaction in ferrets being produced by 5 of these (62.5%); 4 cases without influenza (2 of these being recovered cases from whom the two viruses W. S. and B. W. had been obtained) which were negative in ferrets; and the nasal discharge of a man with a common cold which was also negative. They were also able to induce the typical ferret disease by the swine influenza virus obtained from Shope but found the influenza bacillus did not modify the disease produced in ferrets.

Kairies, as previously mentioned, reported a disease in ferrets of the same type as that described by the English workers which was transmissible from infected fitchets, occurred as a sporadic outbreak in his ferrets and could be transmitted to healthy animals by spraying with materials from a human carrier of influenza bacillus and from a patient with influenza. In all these influenza bacilli were found and were considered etiologically responsible. Kairies (1934) also experimented with a Shope virus preparation (dried lung substance containing a delicate streptococcus) and was successful in inducing this type of disease with the virus and influenza bacilli together and with the virus (containing streptococci) alone. Similar results were obtained with the human influenza virus preparations of dried nasal turbinates (obtained from Andrewes) and from which he grew streptococci, some ferrets, however, becoming ill after the virus alone but not severely so. Glycerinated (Köbe and Shope) virus free from bacteria gave less certain results. He laid particular stress on these non-hemolytic, very small streptococci as of symbiotic importance in assisting the influenza bacillus, having found them in all three preparations of virus and in a number of supposedly pure cultures of influenza bacillus, some of them on media for years, and believed it was significant as an optimal symbiont for the influenza bacillus. He believed that the transfer of human influenza material to ferrets induced in them the influenza peculiar to these animals.

In 1934 Andrewes, Laidlaw and Smith confirmed the results obtained by Shope with ether in ferrets and also obtained similar lung lesions without ether by direct inoculation into the lung. They further added a valuable technical method to the virus study by showing that white mice could be infected with these viruses. Swine influenza virus, after many passages through ferrets and a series of passages through mice, at first directly into the lung but later *via* the nose, became adapted to the mouse so that a high percentage became infected after nasal instillation. The human virus W. S. (obtained originally from the throat of Wilson Smith during an attack of influenza) was similarly adapted from the ferret to the mouse. Although ether is not necessary to produce the lung lesions these are always more severe when it is used. The culture media used in the bacteriologic control of these studies (plain agar, serum agar and blood agar) were not particularly suitable to discover the possible presence of influenza bacilli in any of these lesions. Filtrates from the lungs of these mice, however, produced the disease in a very high percentage of inoculated mice.

The mouse thus became a useful animal in the study of these viruses and particularly for testing the neutralization of virus preparations by antiserum. The technique used for this latter purpose was to mix the virus preparations with the serum to be tested and to inoculate the mixture intranasally into mice. The controls were practically always the virus correspondingly diluted with saline. The serum from hyperimmunized horses taken before immunization was said to have had no effect, but whether it was tested while fresh or months later when the other tests were made was not stated, nor are any details given of this important test. If all of the serum treated mice had been protected against lung lesions and all those untreated had shown such lesions,

this absence of adequate controls might not have seemed so significant, but until more exact information is available about the mechanisms which determine the distribution of materials put in the nasal cavity and about the effect of ether on these it may logically be deduced that serum may change the local conditions and favor the passage of such mixtures to the esophagus rather than to the trachea. The results of Sabin (1935), in his study of the mechanism of immunity to filterable viruses, would indicate that such viruses are not inactivated *in vitro* by antisera. He reported that the virus of pseudorabies, which was equally infective in the guinea pig by either the cerebral or nasal route, was apparently inactivated by a very much smaller amount of antiserum if the mixture were slowly dropped into the nares than if it were injected into the brain. Francis and Magill (1935),[1] in a study of Rift Valley fever virus, reported that when the virus was mixed with immune serum and given by the intraperitoneal route no evidence of infection was observed, but when immune serum and virus was administered by the intranasal route there may be little detectable difference between the protective effects of immune and normal serum. Neufeld and Kuhn (1935), as previously mentioned, showed that under ether mice permit carbon instilled into the nose to be more widely distributed than do guinea pigs.

Francis, in 1934, recovered viruses from the glycerinated sputums of 3 cases of epidemic influenza sent to New York from Puerto Rico. The sputums, washed and emulsified in Locke's solution, were inoculated intranasally into anesthetized ferrets and produced the febrile ferret disease which, after a series of passages using Berkefeld filtrates or unfiltered lung suspensions, resulted in definite lung lesions. Of particular interest was the development of influenza by one of the laboratory workers (S. S.) and the transmission by his bacteria-free nasopharyngeal washings of a febrile disease to ferrets but without pulmonary consolidation. As with the English workers, there were no deaths among any of his infected ferrets. He also was able to transmit the disease to white mice, certain breeds being particularly sensitive, but the lung lesions only developed after passage.

Hoyle (1935) studied the disease produced in anesthetized white mice after intranasal inoculation of certain of these viruses obtained from Andrewes as well as with pathogenic bacteria. The results with the latter are referred to above. He found that the swine influenza virus of Shope, received as desiccated mouse lung, caused lung lesions and on passage these as well as the fatalities among the mice markedly increased. Filtration resulted in a considerable loss in potency, but severe lesions from which no bacteria could be grown were produced with bacteria-free filtrates. Contact transmission of the disease by exposing large numbers of mice to those fatally ill was completely negative. Control mice given sterile broth and normal mouse lung preparations showed no pulmonary lesions. The results with the human viruses were less successful. The B. W. virus (desiccated ferret nasal mucosa) gave an occasional bacteria-free lung lesion in mice. Chamberland L2 filtrates produced at first no lesions, but after passage, using unfiltered preparations, a rise in virulence occurred simultaneously with the appearance of a Gram-negative coccobacillus in the lesions

and preparations. These bacilli passed a Seitz filter. Bacteria-free filtrates gave either no lesions or very tiny non-transmissible ones. The W. S. virus (desiccated mouse lung containing Gram-negative bacilli) gave a variable number of lesions but these all contained small numbers of the small coccobacillus, and on passage this bacillus and the lesions increased. Bacteria-free Seitz filtrates were negative. A 50% glycerol preparation removed the bacteria and this bacteria-free "virus" produced fatal lesions. Hoyle attempted to isolate viruses by direct inoculation with human material from: 1, 5 cases of contagious acute pharyngitis and tracheitis—the unfiltered washings contained Friedländer bacilli resistant to glycerol and no evidence of a virus could be obtained; 2, a case of severe sore throat with negative results; 3, a case of typical acute coryza, washings from which gave transmissible pulmonary lesions with no demonstrable bacteria for several passages, and when bacteria did appear they were readily removed by glycerol without affecting the potency of the preparations. Seitz filtrates were very indefinite. Hoyle believed all these lung lesions induced by virus are examples of aspiration pneumonia, as also are those induced by bacteria and that these cannot be considered as representing a specific illness comparable to human influenza. He also considered the apparently non-bacterial agent he obtained from coryza as similar to the B. W. and W. S. human viruses. He concluded that conditions possessing the epidemic features and high infectivity of human influenza have not been produced in mice by these viruses nor has it been demonstrated that these viruses can be isolated from every case of influenza nor that they are absent from other respiratory diseases.

Francis (1935)[1] believed that at least one of the interpandemic diseases called influenza is causally related to a filterable virus and can be transmitted experimentally to mice and ferrets and that this fact will help to differentiate influenza from other respiratory diseases. In addition to the virus strains from Puerto Rico he has obtained similar viruses from mild epidemics of influenza in New York and Philadelphia and from another assistant in the laboratory. The disease he induced in ferrets was at first only the mild diphasic, febrile one, but after a few passages lung lesions resulted and the disease was more severe. He was unable to transfer the disease directly to mice from man. Francis (1935)[2] further showed that the sera of ferrets, recovered from infection after P. R. 5, P. R. 8 and Philadelphia virus reactions, as well as Andrewes' horse serum (prepared with British strains of virus), were able to neutralize the effect of both the P. R. 8 and the Philadelphia virus when mixed with these viruses and injected into the nose of mice. Normal ferret serum, normal horse serum and convalescent swine influenza serum from Shope (all presumably fresh) had no inhibiting effect in that all of these controls developed well marked lung lesions. These results are very much more definite than any others so far reported.

Laidlaw, Smith, Andrewes and Dunkin, in 1935, gave a detailed report of their experiments with three sera from horses immunized with the turbinates or lungs of ferrets infected after human or swine virus inoculations. There were present in these sera precipitins for normal ferret serum, hemolysins for ferret cells and complement fixing antibodies with ferret lung emulsions. In all those tests which are

recorded in detail the controls were as above only virus in saline, although they say the normal sera did not neutralize the virus. Mice were used in nearly all the studies because the virus does not spread from animal to animal in this species and larger numbers can be used. The W. S. was the human virus used in most of the tests. They noted that passage virus ultimately leads to lung abscess in some mice and that Gram-negative, bipolar bacilli were sometimes found. The virus varied considerably in different tests so that often some of the controls survived or showed minimal lesions. In the experiments with passive immunity by intraperitoneal injection of serum the control animals were untreated. The tests were rather irregular but the intraperitoneal injection of antiserum 24 hours after the nasal inoculation of virus seemed to be beneficial. Various fractions of the antiserum, particularly pseudoglobulins were tested. They noted that the mice injected with large doses of horse serum often became ill at once, that the concentrated pseudoglobulin seemed more toxic and they found this was caused by agglutinins for mouse red blood cells in the horse serum there being more of these in the concentrated serum. This temporary reaction after intraperitoneal injection must be considered as affecting the resistance in the respiratory mucosa, perhaps by reflex action, and may very well be a factor in preventing the establishment of the virus, although the authors considered it an undesirable side action of the antiserum. Normal horse serum giving this same reaction should have been, but was not, used in the controls and, failing such controls, the results cannot be fully accepted as due to pure antibody action. The lesions found in the mice which received serum 24, 48 and 72 hours after the virus and lived are considered as due to the effect of the virus before it was neutralized, but no suggestion is made that the serum itself may have contributed to these lesions. The results using a large number of mice in each experiment are similar. Of 25 mice given virus alone, 5 lived (20%); of 24 given virus by nose and 24 hours after serum intravenously or intraperitoneally, 16 lived (66.6%), and of 25 given serum 48 hours after the virus, 15 lived (60%). They said that a pseudoglobulin fraction made from normal horse serum had no curative effect but they did not say that this serum had or had not agglutinins nor what its source was. The authors are convinced that certain epidemics of influenza are caused primarily by a virus infection.

Smith, Andrewes and Laidlaw (1935) experimented on methods for immunizing ferrets and mice. Ferrets after recovery from infection were resistant for at least 3 months, after which the immunity slowly waned. In this latter period there remained virus-neutralizing antibodies in their serum but the nasal mucosa was still susceptible to virus. Subcutaneously injected virus gave these animals once more a full resistance. They were able to produce a partial immunity in ferrets by subcutaneous injections of living or formolized virus so that antibodies appeared in the blood and after intranasal inoculation of virus the lungs were not affected. Ferrets developed lung lesions when swine influenza virus was given in the nose with, and often without, ether. Neither of the human viruses gave lung lesions in ferrets at first, but W. S. was modified by serial passage using ether until it also

did. In all these experiments the controls were untreated before the test and in the titration for neutralizing antibodies the controls were given virus in saline. Mice immunized by two fortnightly subcutaneous or intraperitoneal living virus injections and tested 8 days after the last, showed no symptoms, but 7 of 12 had lung lesions and in 5 of these the lesions were of the same extent as in 2 of 6 controls. The controls received no previous treatment and were all ill after the test virus inoculation. In a larger group after subcutaneous vaccinations and tested in 10 days only 2 of 24 showed a small lung lesion, after two similar vaccinations and tested 23 days later 5 of 20 gave slight to moderately severe lesions while of 24 controls with no previous treatment 9 gave similar lesions, 10 none and 5 severe fatal lesions. The evidence in this report for the differences between the swine and the human virus is based on incomplete neutralization by heterologous sera. Eleven human convalescent, 6 of 8 normal, and 5 of 6 human placental serums neutralized the W. S. virus and 2 human convalescent and 1 normal serum neutralized the swine virus while 1 human placental serum did not. They hope that a vaccine applicable to humans may be developed.

Francis and Magill (1935)[2] gave a warning that it is necessary to quarantine newly bought ferrets for 2 to 4 weeks, since some of them develop purulent rhinitis and may carry hemolytic streptococci or Gram-negative bacilli. These workers found one shipment of ferrets resistant to experimental virus infection, another lot susceptible and a third on arrival exhibited nasal discharge—all these animals coming from the same breeder. Some of this latter group were also resistant to active virus and the virus after inoculation could not be recovered from them, while with others a moderate fever and other symptoms lasting 3 to 4 days followed inoculation, but again the virus could not be transmitted by inoculation of lung or turbinate suspensions into susceptible ferrets. Two of these ferrets whose serum neutralized the virus were given the virus per nose with negative results, and the lungs and turbinates of one of these failed to give disease to a normal. They assumed that these ferrets had become immune in some unknown way and it is unfortunate that no ferret virus was obtained from any of them at the time they exhibited a nasal discharge. Of course it is just possible that this lot of ferrets was recovering from distemper. (See a later discussion.) These workers succeeded in producing serum-neutralizing antibodies in rabbits which species is not susceptible to infection. Mice were also immunized by subcutaneous, followed by intraperitoneal inoculation of living virus in lung tissue, and controls similarly inoculated with normal lungs developed no such immunity as shown by the fact that after intranasal inoculation of virus all the latter showed lung lesions, and none of the former. Neutralization tests with the serum of patients before and after recovery from influenza, pneumonia and the common cold suggested a specific response to infection with the virus of influenza only in the case of influenza. In 3 influenza patients the sera neutralized the virus for mice during convalescence and 6 months later, but not in the acute stage. In 8 pneumonia cases the power of the serum varied from complete to almost no neutralization, but in only 1 did this increase during convalescence. In 4 cold cases the serum before, during and after the affliction remained the same, and in 1 it gave complete neutralization in each test.

Laidlaw (1935) in his Linacre lecture on Epidemic Influenza gave a number of interesting facts. The virus was destroyed at 56° C. in 1 hour, and was resistant to drying and storage in 50% glycerol. It was only recoverable from the lungs and upper respiratory mucosa. In animals without ether it was not fatal. Certain streptococci increased its severity but H. influenzæ did not modify the disease. There was no evidence that in this last observation fully virulent cultures were used. He explained the lack of contagiousness in mice on the bases that the nose was unaffected and sneezing did not occur. (In the epidemiology of influenza, however, sneezing or coughing is not the sole explanation of the high contagiousness.) The failure to obtain virus from all cases of influenza he believed is due to an insufficient amount of virus in the nasopharyngeal washings, because the ferret is less sensitive than man, or on account of the varied resistance of the human population. His final view is that the virus may cause the mild short disease and that with the hemoglobinophilic bacilli the sinusitis, purulent bronchitis and pneumonia follows—if the bacterial factor were varied, he said, this would explain much. He suggested that a variant of the local virus may be the cause of epidemics.

Elkeles (1935) was successful in transmitting human influenza to suckling pigs, using intranasal inoculation of the virus before and after ferret passage. The pathologic picture produced in pigs was the same as that described for ferrets by the English workers, but the course of the disease was more severe when virus and influenza bacilli were used. The influenza bacilli alone had no effect. He advised the use of suckling pigs for these virus experiments as being more suitable than ferrets since they react more easily.

Francis and Magill (1935)[3] reported the cultivation of the P. R. 8 strain of human virus after 44 passages in white mice. Lung preparations in Tyrode's solution were centrifuged and filtered through a Berkefeld V candle and the bacteria-free filtrate seeded into chick embryo Tyrode's medium, and serial transfers made every 48 hours. Mice inoculated intranasally with the 10th and up to the 20th subculture developed pulmonary lesions. Cultures were also passed through mice and again cultured from these with similar results. A ferret also responded typically to an inoculation from the 7th culture. The cultured virus was inhibited by the sera of ferrets recovered from infections with the P. R. 8, the Philadelphia or the new Alkaska strain of virus and not by normal ferret serum. The uninoculated medium was entirely innocuous for mice. They noted certain alterations in the immunologic characteristics of the virus after repeated cultivation *in vitro* and this is to be investigated.

Noble and Brainard were able to produce symptoms of a mild respiratory disease in 4 of 12 ferrets by inoculation with filtered bacteria-free nasal washings from human cold cases and apparently to transmit this condition from a ferret to a human being. One attempt to transmit it serially from ferret to ferret was unsuccessful.

Summary of the Influenza Virus Studies. 1. The virus of swine influenza is contagious by pen contact in swine. It is not definitely so in ferrets or mice.

2 The pure virus disease in swine is relatively mild but the epi-

demiologically complete disease follows the mixture of virus and influenza bacilli.

3. The virus obtained from man also produces the characteristic disease in swine under the same conditions as the swine virus.

4. Human viruses, giving a disease in ferrets and from ferrets in mice, have been obtained from various parts of Great Britain and in America from Puerto Rico, Philadelphia, New York and Alaska. Immunologically all these strains act alike.

5. The pure virus disease in animals is mild and the epidemiological evidence that the responsible virus is the causative factor in human influenza is incomplete. No clear proof has been given that influenza bacilli or other bacteria are involved in the disease in animals but little has been done with fully virulent H. influenzæ in this phase of the problem.

6. The virus lung lesions without, but particularly after, the preceding use of ether are not accepted as specifically a virus lesion.

7. The virus disease in ferrets is not specific for virus infection but would seem a type of response in the ferret to a number of agents.

8. The virus has not been obtained from all cases of clinically diagnosed influenza and the arguments that the negative results are due to faulty diagnosis, to scarcity of the virus, or to varying resistance applies equally well to the influenza bacillus theory. There can be no doubt that a variety of influenza-like diseases has a variety of etiologic agents and the problem is primarily whether or not pandemic influenza has a constant etiology.

9. Viruses with very similar characters have been obtained from other diseases such as the common cold. These might be, of course, less virulent strains of a common virus. This is the only evidence that a possible reservoir for the virus in interepidemic times has been found, and is obviously rather weak. There is no method today available for discovering viruses in non-virulent form.

10. The investigators who have used the immunologic evidence as favoring the virus theory have not sufficiently analyzed: the anatomic and physiologic background in the intranasal neutralization experiments and in the passive immunity tests; or the reflex effects of extra-respiratory injections; or the possible sensitizations and the effects of protein or foreign serum shock; nor have most of the controls been satisfactory.

11. No adequate evidence to account for the toxicity of clinical influenza has been suggested.

Nevertheless, most valuable data are now available from these virus studies of influenza bearing on the resistance of recovered animals and the presence of neutralizing antibodies in relation to this and to recovery in man, so that the virus theory is certainly gaining ground and may serve at least to differentiate certain respiratory diseases from others. Very few other epidemics have been adequately explained even when the etiologic factors are known so that we must not demand too much at this early stage of the virus investigation of influenza.

Other Virus Diseases of the Respiratory Tract. *Distemper.* The use of ferrets for the isolation and identification of the virus of dog distemper by Dunkin and Laidlaw, the natural susceptibility of these

animals to distemper and their predominant use in the study of the human influenza virus make it advisable briefly to refer to certain reports bearing on a possible relationship between the two viruses. Distemper is usually a respiratory disease and has many clinical and epidemiologic resemblances to influenza. Bemelmans (1932) considered these two diseases as well as pleuropneumonia of horses as practically identical, largely, it is true, on theoretic and philosophic grounds. The virus, however, produces the disease in animals after subcutaneous and other routes of injection, and in infected animals the virus is found widely distributed in the blood and other tissues.

Nicolle (1931) inoculated subcutaneously a man, a monkey and a young dog with defibrinated blood of a dog ill after inoculation with distemper virus. The dog developed the typical febrile disease on the fourth day. On the sixth day blood taken from the man and the monkey (neither having shown any symptoms) was injected intraperitoneally into two dogs under isolation. The dog which received the blood from the man developed the disease and its blood was infective for two other dogs. The dog receiving the monkey's blood remained well. Nicolle concluded from this evidence that man can be infected with this virus but without showing any symptoms, and that under certain circumstances he can play the rôle of a virus carrier particularly dangerous, perhaps, because unrecognized. The philosophic conclusion he drew from these observations was that dog distemper had been a primitive disease of man effaced little by little from human pathology as a result of the hereditary immunity following repeated attacks, but that the disease is relatively new in the dog and attacks it with severity. It is unfortunate that nasopharyngeal washings were not tested for the virus in this experiment. On the basis of this report Remlinger (1933) suggested that sporadic distemper in dogs may be derived from human carriers and that the blood of man, probably containing antibodies, might be used to treat infected dogs. I have not found any evidence that such has been tried. Norr (1935), in a study of influenza-like diseases of animals, referred particularly to distemper which attacks dogs, cats, ferrets, monkeys and other animals. He said there had been a steady increase in Munich since 1934 of the nervous form of dog distemper—the most dangerous form of the disease—and considered the possibility that such an increased virulence might be related to outbreaks of human epidemic influenza. Both diseases are readily transferable to ferrets. He suggested that the serum of dogs recovered from distemper be tried in severe cases of human influenza and in any case that correlated facts be collected bearing on the periodic coincidences of these diseases in man and animals. Eichhorn and Pyle (1934) partly confirmed the results of Smith, Andrewes and Laidlaw, using a virus brought back from England which, on passage through ferrets, lost its infectivity for ferrets. All the ferrets recovering from the virus disease were not immune. A new supply of virus remained active and had been passed through a series of 30 ferrets. Two ferrets were inoculated at each passage and one was allowed to recover so that many recovered ferrets were available. Eleven of these latter were used for testing, by injection, a canine distemper virus and they were surprised to note that there was a delay in the onset of the disease from the usual

incubation period of 9 to 10 days to one of 13 to 17 days and 2 ferrets were apparently fully immune. A second series of 11 ferrets were given influenza virus by nose, and after recovery were injected with a known fatal dose of canine distemper virus. Four were completely immune, 4 others showed questionable immunity and death was delayed in all the others. Further studies by these authors on this suggestive problem are promised but I have not seen any later report. Schaaf (1935) also found that a previous infection of the ferret with the virus of human influenza increased the resistance of this animal to the virus of dog distemper in that the disease was less acute and death occurred very much later than in the controls. Smith, Andrewes and Laidlaw (1933) emphasized the importance of quarantining all ferrets for 14 days to prevent a latent distemper from giving rise to serious confusion and, in 1935, they had one of their experiments ruined by an outbreak of distemper in their ferrets. It would be interesting to know whether or not the spontaneously immune ferrets which Francis and Magill (1935)[2] encountered were recovering from distemper.

Other Viruses. It is scarcely necessary to do more than mention the lung lesions of other virus diseases. Psittacosis is well known with its lobular confluent pneumonia and clinical resemblance to influenza. The similarity of smallpox vaccine virus pneumonia in rabbits (Muckenfuss, McCordock and Harter) to epidemic influenza and interstitial bronchopneumonia in man has been described by McCordock and Muckenfuss. They produced two types—a hemorrhagic after concentrated, and an interstitial bronchopneumonia after dilute virus—and they discussed the resemblances of the former to the findings in acutely fatal cases of epidemic influenza and of the latter to the lesions accompanying influenza, measles and whooping cough in man, and in some cases of distemper in dogs. The latter type was only reproducible when bacteria were also injected with the virus, but they did not consider this lesion in any way specific for a particular virus or bacterium. Francis (1935)[1] referred to the confusion between certain cases of yellow fever and influenza. Francis and Magill (1935)[1] reported 3 cases of laboratory infection with the virus of Rift Valley fever in all of which a clinical diagnosis of influenza had been made. The disease was differentiated by: the demonstration of the virus recovered by intranasal inoculation of ferrets; the fact that it was found, and produced lesions, in other tissues than those of the respiratory tract, and further by the serum neutralization tests in mice.

General Discussion. The virus of influenza does not form inclusion bodies, nor does it produce as lasting an immunity as most other virus diseases. Until we know a great deal more about the nature of these disease producing agents our attitude towards the evidence should be extremely critical, and only the most carefully designed and controlled experiments should be accepted. It is a time for collecting facts not for drawing conclusions. A filterable virus as Hyde conceived it (1935) is an agent of particulate nature, of ultramicroscopic dimensions, it passes filters that retain vegetative forms of parasitic life, can be passed in series on sensitive hosts, produces characteristic inclusion bodies, cannot be cultured on lifeless media and would be unknown were it not for the changes produced in the body of animals and plants. The

limits of variation of viruses in different hosts and the modifications which result from differences in virulence are largely unknown, nor do we know if they exist in a quite avirulent and therefore undetectable form in carriers, nor whether these can be brought into activity by predisposing conditions.

The evidence for the three suggestive theories for the primary etiologic agents in influenza—bacteria, virus and virus plus bacteria—is here presented, and it is hoped that many of the unsolved phases of the problem will be more adequately dealt with in the event of another pandemic. The ideal method would be to have equally enthusiastic investigators of the different views study the same cases independently, since there are many hiatuses to be filled before the etiology of influenza can be established.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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IMPORTANCE OF IMMUNIZATION IN PREVENTIVE MEDICINE.*

The Common Communicable Diseases.—The field covered by the title above is one in which much has been accomplished and much is hoped for, but in which there have been many disappointments. It is a remarkable fact that smallpox vaccination, the first of the immunological procedures developed, should also have been the most successful, although it was applied long before immunology in its modern implications was known. It is also remarkable that immunizations against rabies, diphtheria, and tetanus were among the very earliest developments in the field of immunity and these, in a general way, are highly successful measures. The success attending these early applications of immunity in preventive medicine may account for the almost childlike faith with which many of the later developments have been welcomed, faith that often was converted into disillusionment on the basis of further observation. In considering the application of immunological procedures from the public health point of view, it is necessary to take into account factors other than the essential effectiveness of the proced-

* This material covers the substance of several addresses to medical groups. It has not been arranged with the customary references, which, however, can be supplied by the author on request.

ure. It would be foolish to attempt to immunize the entire population against whooping cough which practically is important only in the early years of life, or to immunize infants against typhoid fever since this is chiefly a disease of older age groups. This illustrates the importance of the age factor in planning an immunization campaign. Again, the disease may be one of so low an incidence in the community that it would be inadvisable to apply serum or vaccine prophylaxis generally. Obviously, it would be inexpedient to attempt general vaccination against rabies even if we had the means of doing this that were perfect—hence we vaccinate only those who have been definitely exposed. Finally, in this connection, we must remember that substantially all immunization procedures have certain risks associated with them, risks that must be carefully weighed lest we incur hazards in excess of those we seek to avoid. With these preliminary considerations in mind we may now turn to an appraisal of the status of certain procedures in the light of experience up to the present time. The various diseases will be considered somewhat in the order in which immunization procedures for them have been developed. No reference will be made to therapeutic application of immunological procedures.

Smallpox.—The question often is asked as to the duration of smallpox immunity. It has been a controversial point since the days of Jenner. A safe rule would require vaccination before a child had reached the age of 6 months, again before the age of 6 years, and thereafter only in the presence of an epidemic or when there is a threat of exposure. There are certain complications following smallpox vaccination that have attracted much attention during the last two or three decades. These complications were relatively unimportant as causes of disability and death but were taken as a ground or criticism on the part of anti-vaccinationists.

Postvaccinal Tetanus.—This, now very rare, was at one time sufficiently prevalent to be taken into consideration by all concerned with vaccination. The source of the infection, even after much investigation, still remains unknown. The disease was of marked severity, the death rate being 90% or even more. The incubation period, counting from the time of the insertion of the vaccine virus, was rather long, usually about 3 weeks. In a careful investigation by Dr. Armstrong of the United States Public Health Service, it was demonstrated that postvaccinal tetanus was found only when a dressing or shield was applied to the site of vaccination, although, of course, not all such applications were followed by tetanus. So, to prevent this complication, avoid dressings.

Postvaccinal Encephalitis.—The etiology of this is unknown. Perhaps the most plausible view regards it as virus infection remaining silent in the community and in the individual until something happens to activate it, the "something" being an infectious disease, in this case vaccinia. The symptoms usually come on from 7 to 14 days after the insertion of the vaccine virus, and essentially they are fever, headache, vomiting and other symptoms directly referable to the central nervous

system. The condition often is overlooked as it is easily mistaken for other acute nervous system infections, especially poliomyelitis or meningitis. This complication is extraordinarily rare in children under 2 years, hence the best safeguard is to vaccinate as early in life as possible. In some countries this complication has been so prevalent that local action has been taken permitting the restriction of vaccination.

Septic Infections.—Much less is known about these than about the preceding complications, but employees' compensation and other statistics attest their existence. Within recent years certain new methods for the propagation of vaccine virus have been introduced. While the calf vaccine which has given long and efficient service still remains the most popular agent, artificially cultivated vaccine virus which is propagated in the chick embryo tissue or the living chick embryo is being tried. It is too early to make a definite appraisal of the value of this type of vaccine virus.

Typhoid Fever.—Most of the information as to the efficiency of typhoid vaccine comes from military experience where the evidence indicates that it has proven extremely satisfactory. However, the experience in civil communities has been less satisfactory—so much so that a few years ago the American Public Health Association appointed a committee to study the whole subject of typhoid vaccination. When this report is completed and made public doubtless we shall have better information on the subject.

There have been modifications in the dosage of the typhoid bacillus and in the components of the vaccine as to the paratyphoids. It scarcely can be said that any one preparation is to be regarded as standard. That there has been dissatisfaction with the results of typhoid vaccination is shown by the studies being carried on by various research workers here and abroad in an effort to improve the vaccine. These studies are related to our growing knowledge of the complex nature of antigens and to the antigenic peculiarities of different strains of the same bacterial species. There, of course, has been a marked and gratifying reduction in our typhoid fever rates in recent decades, but it is very doubtful that immunization has been an important factor in bringing this about.

Diphtheria.—In connection with diphtheria prophylaxis it must be remarked that the disease takes its chief toll in children under the age of 6 and if prophylactic procedures are delayed until the child enters school the best opportunity for preventing infection has been lost. Passive immunity with diphtheria antitoxin once played an important rôle in the prevention of the disease. This practice is limited now to the few occasions in which it is impossible to keep those in contact with known virulent infection under close medical observation. In all diphtheria prophylaxis the importance of the Schick test must be borne in mind, especially after the immunization procedure has been completed. The mere injection of a person with one or more doses of a prophylactic is not a guarantee that immunity will be induced. It is appreciated, of course, that the Schick test is not an infallible index of diphtheria

immunity, but for practical purposes it may be considered as giving most useful information. The two preparations most in use at the present time are the Ramon toxoid, which is given in 2 or 3 doses at intervals of 3 or 4 weeks, and the more recently developed, refined alum precipitated toxoid which is given ordinarily in one dose. The latter, of course, has a great advantage in requiring but a single injection. On the other hand, it occasionally is followed by rather annoying indurations and even abscesses and thus far the research workers have failed to develop a means whereby this complication may be avoided.

Scarlet Fever.—Early work bearing on the streptococcus as the etiologic agent of scarlet fever was rather inconclusive but the work of Doctors Dick, Dochez and others has put the whole subject in a different light and on a sound foundation. Passive immunity induced by the injection of scarlet fever streptococcus antitoxin is believed to be inadvisable generally because of the low incidence of scarlet fever among contacts and the likelihood of serum reactions which appear to follow scarlet fever antitoxin somewhat more frequently than other antitoxins. Within very recent years serum from those convalescent from scarlet fever has been used for passive immunity; much success is claimed for the procedure but it is too early for final appraisal of the practice. Active immunity induced by means of several injections of a toxic filtrate developed from the hemolytic streptococcus of scarlet fever appears to be an effective measure for the prevention of the disease. This method of prophylaxis requires 5 injections in addition to a preliminary Dick test to determine susceptibility and another Dick test after the injections have been given to determine whether the immunization has been successfully accomplished. This means that the physician must see the patient seven times. Most health departments have found it impracticable to attack scarlet fever in this manner, but it would appear that this is peculiarly a field where the private physician might recommend immunization of susceptible children among his clientele.

Whooping Cough.—The evidence is most contradictory on the efficiency of whooping cough vaccine. The disease has its prevalence chiefly in those of tender years, the highest mortality being during the first 2 or 3 years of life. The older whooping cough vaccine preparations probably were of little or no value. Certain newer preparations that have come into use in recent years seem to offer more promise, but even these can hardly be said to have become well enough established to justify widespread general application. Stress is laid on certain details of manufacture, which perhaps cannot be practiced readily in large scale production.

Measles.—It seems to be quite clear that it is practicable to prevent measles by giving to exposed children serum from persons recently convalescent from the disease, or even serum or whole blood, of adults. The dosage and time of administration of the serum must be chosen carefully to secure the most favorable results. If the serum is given immediately after exposure, an attack of measles is likely to be avoided and the child will have only a temporary immunity. If it is given from

5 to 8 days after exposure, a mild attack of measles which is practically free from danger frequently ensues, resulting in a lasting immunity. Within recent months commercial preparations of human placental extract have been developed for use in measles prophylaxis; apparently the effect is much the same as that of convalescent serum.

Influenza, the common cold, meningitis, pneumonia, and poliomyelitis are all still beyond any practicable means of prevention, by induced immunization.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA,
SESSION OF JANUARY 20, 1936.

The Effect of the Adrenotropic Hormone of the Anterior Pituitary Upon Hypophysectomized Depancreatized ("Houssay") Cats.—C. N. H. LONG and F. D. W. LUKENS (George S. Cox Medical Research Institute, University of Pennsylvania). The preparation of the purified adrenotropic hormone has been described by Collip, to whom we are indebted for our supply of the extract. Collip and others have shown that this extract is anatomically specific in causing a regeneration of the adrenal cortex following the atrophy which takes place after hypophysectomy in the rat. It is practically free of all other pituitary hormones as determined by anatomical methods. No metabolic studies have been reported with it to our knowledge. It does not restore hypophyseal cachexia even when adrenal regeneration is accomplished and produces no effect on the adrenal cortex of normal animals. The extract has been tested by us on 4 fed and 2 fasted Houssay cats in excellent condition. The fed cats were on a constant diet throughout the experiment. In both fed and fasted Houssay animals there was an increase of glucose and nitrogen excretion during extract administration, amounting to as much as three times the value of the excretion before and after the administration of the hormone. The nitrogen excreted was at all times more than enough to account for the glucose obtained. Ketonuria was absent throughout, since any ketogenic activity of the extract had been removed by boiling before use. The conclusion is reached that the adrenotropic hormone of the pituitary exerts a stimulating influence on protein metabolism. As far as glucose and nitrogen are concerned, these results are compatible with our previous reports of the effect of hypophysectomy and adrenalectomy on pancreatic diabetes.

The Effect of Adrenalectomy Upon the Response of the Rat to the Ketogenic Principle of the Anterior Pituitary.—EDITH G. FRY (George S. Cox Medical Research Institute, University of Pennsylvania). The increased ketonuria developed by normal, fasted rats in response to

injections of alkalin extracts of the anterior pituitary* was greatly reduced by adrenalectomy, whether the animals were maintained after operation on physiologic saline or on active extracts of the adrenal cortex. However, if the presence of accessory cortical tissue was either identified microscopically or indicated by long survival of the rat after withdrawal of saline or cortical extract therapy,* increased ketonuria resulted.

Long and Lukens have found that the spontaneous ketonuria of depancreatized cats was suppressed by hypophysectomy or adrenalectomy. Two explanations may be offered for these findings: *a*, The presence of the adrenal cortex mediates this ketogenic activity of the anterior pituitary; *b*, adrenalectomy suppresses the usual ketonuria by inducing structural and functional alterations in the anterior pituitary.

Saline therapy for adrenalectomized rats may not have prevented such alterations in the anterior pituitary, but cortical extract treatment which permitted normal growth should have prevented any such changes. Since the increased ketonuria was suppressed in both series, these results favor the first view that the adrenal cortex is directly concerned with the ketogenic activity of the anterior pituitary extracts employed.

Preliminary experiments indicate that rats respond to the same anterior pituitary extracts as well following thyroidectomy as before operation.

A Study of Gastric Emptying with an Open Tube in the Pylorus; Results with Liquids Including Olive Oil and N/20 HCl.—J. E. THOMAS and J. O. CRIDER (Laboratory of Physiology, Jefferson Medical College). Observations have been made on two dogs, provided with cannulated gastric and duodenal fistulas, under the following conditions: 1, Without apparatus (normal controls); 2, with an apparatus in the pylorus which maintains a 7-mm. opening, and 3, with an apparatus identical to the other externally but which does not open the pylorus (dummy controls). The apparatus consists of an aluminum tube held in the pylorus by means of narrow flanges and by rubber tubes passed through the gastric and duodenal fistulas. The cannulas are stoppered around the tubes so that leakage does not occur. Lateral openings in the tubing near the pylorus on each side complete the free communication between the stomach and duodenum.

The rates of emptying of normal saline, N/20 HCl and of olive oil were studied under each of the above conditions. There was no significant difference in the emptying times with the pylorus open as compared with the controls (normal and dummy) except that the emptying time of oil appeared to be prolonged somewhat when the pylorus was kept open. The following table gives the average emptying times so far recorded:

	Saline.		HCl.		Oil.	
	Dog 1. *Min.*	*Dog* 2. *Min.*	*Dog* 1. *Min.*	*Dog* 2. *Min.*	*Dog* 1. *Hrs.*	*Dog* 2. *Hrs.*
Normal controls	18.5	21.25	41.6	48.3	4.66	3.0
Dummy controls	17.5	22.5	44.4	45.0	4.2	3.0
Pylorus open	22.0	20.0	47.8	45.0	5.0+	4.0+

* We are indebted to the E. R. Squibb Company and the Upjohn Company for generous supplies of anterior pituitary and adrenal cortical extracts.

Experimental Pulmonary Edema.—Virgil H. Moon and David R. Morgan (Laboratory of Pathology, Jefferson Medical College). Pulmonary edema is found regularly at postmortem in man when the shock syndrome has preceded death. It is seen frequently in experimental shock when death was somewhat delayed. These facts suggested means for producing pulmonary edema experimentally. Shock with delayed death was produced by implanting muscle substance in the peritoneal cavity, by sublethal burns, by the injection of bile and of bile salts intravenously or intraperitoneally, by intestinal obstruction, barbital poisoning, and by repeated subcutaneous injections of histamin in dogs. In each instance hemo-concentration of 30% to 40% developed and the postmortem findings were those regularly present following death from shock.

Marked pulmonary edema was present in each animal so treated. The edema fluid had high specific gravity closely approximating that of the blood serum. Beginning pneumonia was seen frequently in the dogs which survived treatment longer than 4 days. The lungs were closely similar to those seen in man following burns, severe infections, intoxications, and so forth. Such edema results from increased vascular permeability and its mechanism of development apparently is integral with that of shock.

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